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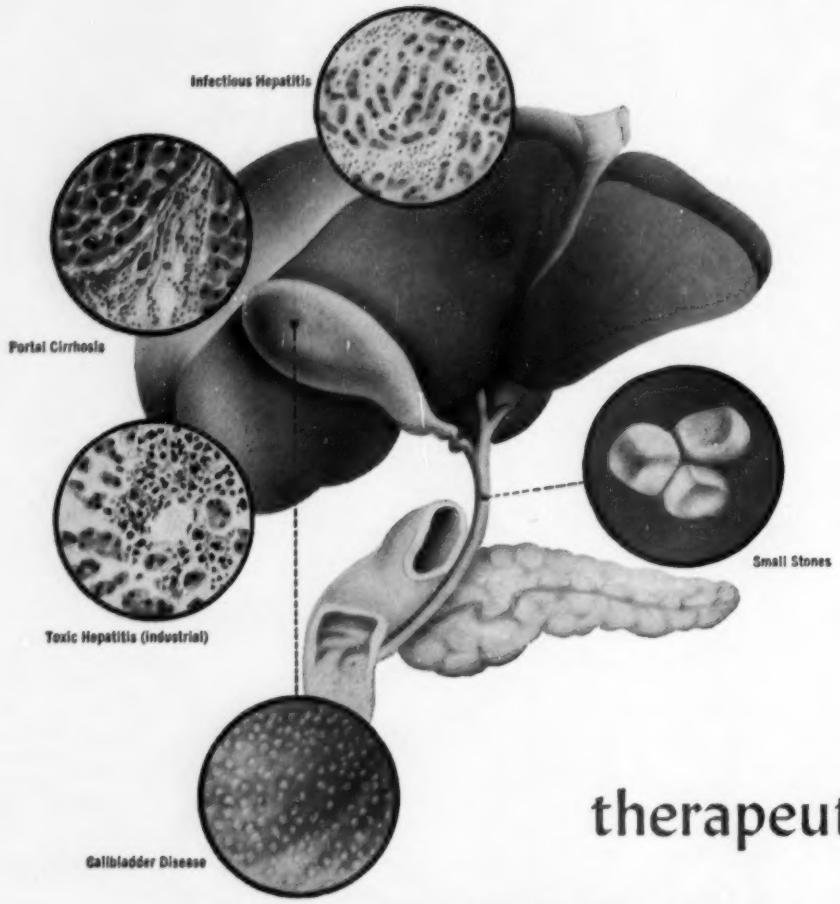

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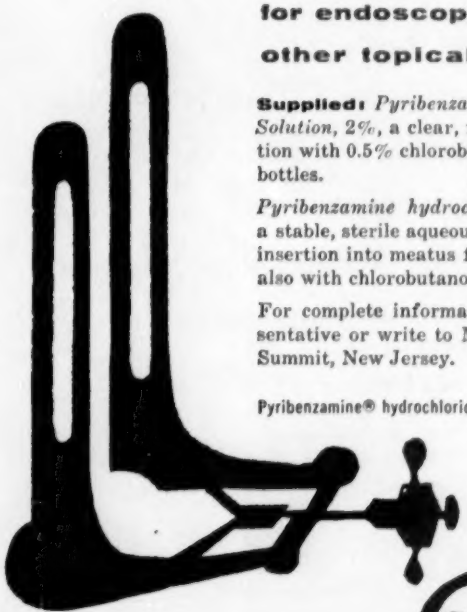

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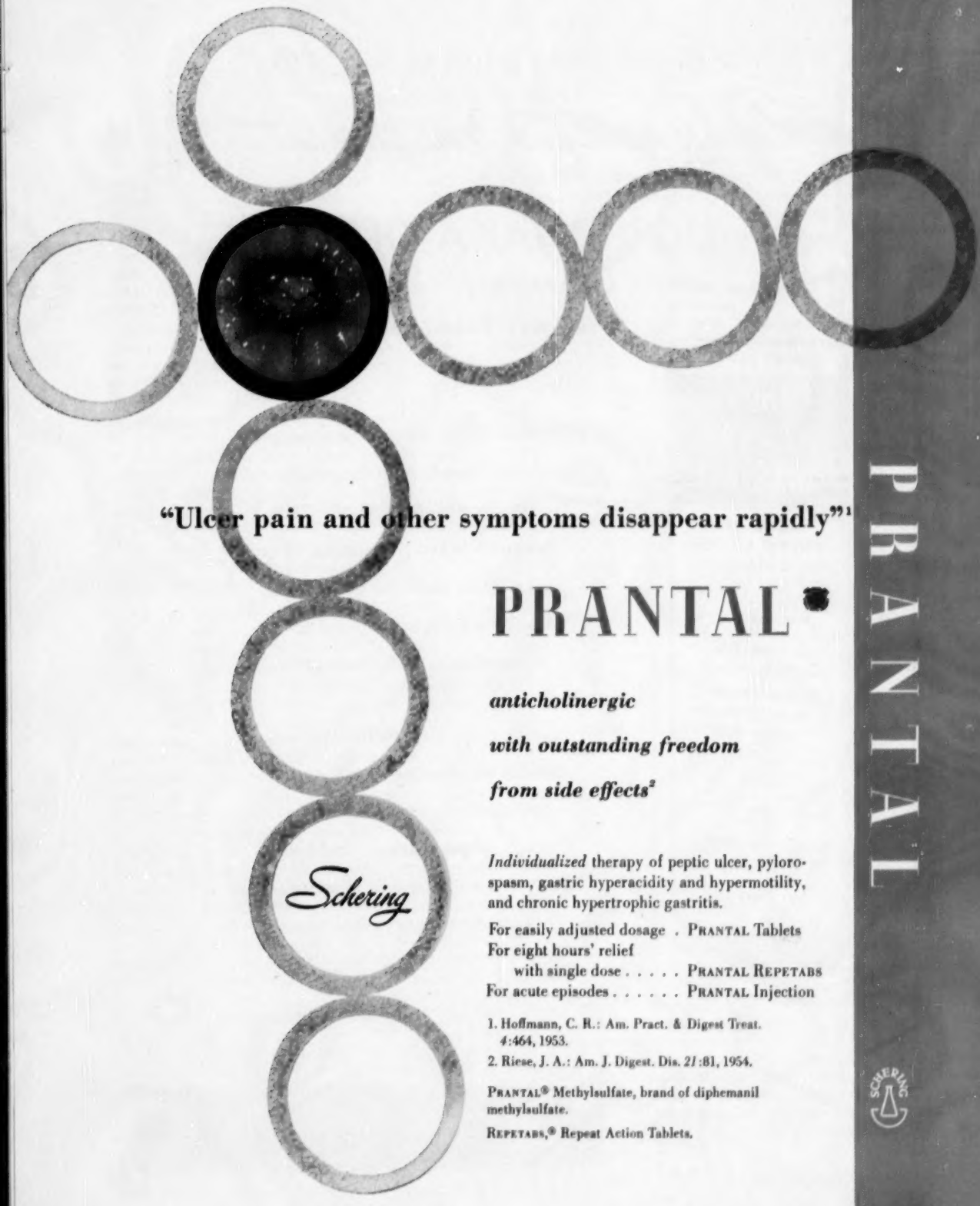

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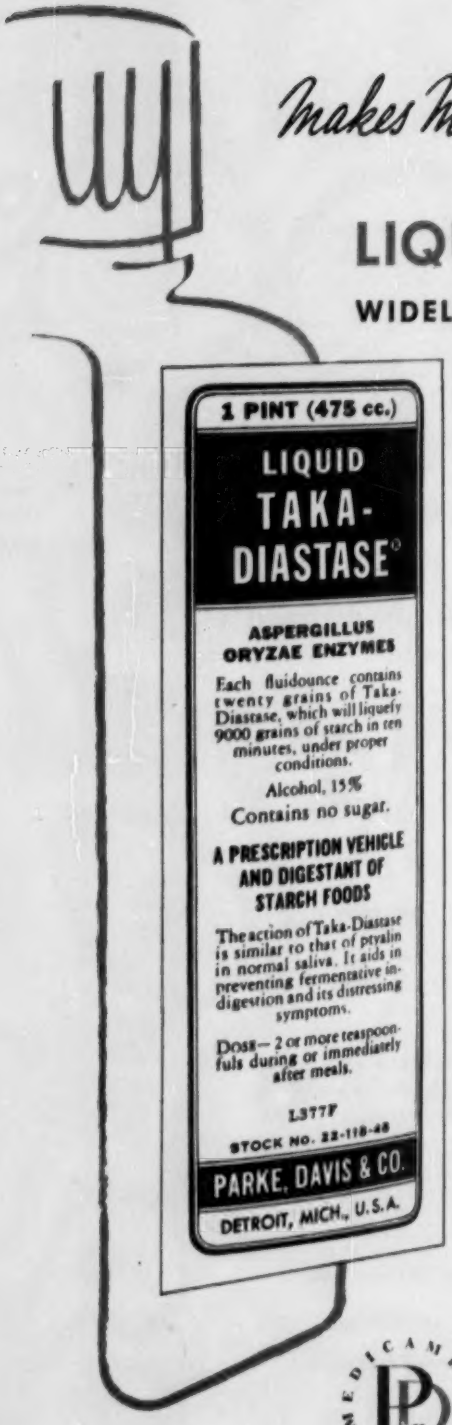

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PYRUVIC ACID METABOLISM IN OBESITY

A. W. Pennington, M.D., Wilmington, Del.

MANY YEARS ago Zuntz reported the case of a man who gained weight on a high carbohydrate diet and lost weight on a high fat diet of equal caloric value (1). Benedict and Milner (2) confirmed this observation with a subject who did a uniform amount of work each day on a bicycle ergometer. Lyon and Dunlop (3), using 1000 calorie diets in a series of 14 obese people, found a much greater loss of weight when a large proportion of the calories were derived from fat than when they were derived from carbohydrate. Anderson (4) challenged this finding and concluded from his own experiments that the difference in weight loss must have depended on a difference in salt intake. Kekwick and Pawan (5) however, have recently confirmed the results of Lyon and Dunlop. Keeping the salt intake constant, they found far greater weight loss on 1000 calorie diets in which 90 per cent of the calories were derived from fat than on 1000 calorie diets in which 90 percent of the calories were derived from carbohydrate. The experiments were carefully controlled and they showed that the larger amounts of fat were well-absorbed by the alimentary tract. Ohlson (6) in a series of studies on obese college women, has found more weight loss on 1500 calorie diets containing much fat than on 1200 calorie diets containing much carbohydrate.

The greater efficiency of high fat diets in weight reduction has often been puzzling in view of the widespread acceptance of Rubner's "isodynamic law." This law, which stands dimly at the basis of current nutritional theory, holds that, calorie for calorie, carbohydrate and fat are interchangeable in respect to their effects on the energy balance (7). Theory and experimental facts have usually been reconciled by explanation based on shifts in the water balance. Most investigators have found a loss of water from the body when the diet is changed from carbohydrate to fat (8); Newburgh (9) however, reported the opposite. To answer the question whether the loss of weight occasioned by a change from carbohydrate to fat in the diet depended entirely on loss of water or whether it was partly due to increased oxidation of nutrient materials, Benedict applied calorimetric experiments (10). His studies of two normal men showed a much greater oxygen consumption when the diet was high in fat. Ohlson found that obese subjects on low calorie diets showed less decline in metabolism when more fat was used (6) and Young's clinical studies gave similar results (11). There seems, therefore, to be reasonable evidence that fat and carbohydrate are not always identical in their effects on the energy balance. On high fat diets the obese appear to expend more energy and to store less fat than on high carbohydrate diets.

Studies of the effect of protein on the energy balance have also been enlightening. High protein diets have often been advocated as especially valuable in weight reduction by virtue of the high specific dynamic action of protein. Controlled experiments, however, do not support this view. Lyon and Dunlop (3), using isocaloric diets, found more weight loss when most of the calories were derived from fat than when they were derived from protein, and this has been confirmed in a very definitive manner by Kekwick and Pawan (5). The greater energy expenditure to be expected from the high S.D.A. of protein appears to be offset by some other factor in the obese. Rolly (12) and Wang, Strouse and Saunders (13) found the S.D.A. of protein defective in the obese, indicating the presence of some metabolic alteration from the normal. They found the S.D.A. of carbohydrate defective also, while the S.D.A. of fat was normal.

Lyon and Dunlop noticed that weight loss appeared to be inversely related to the amount of glycogenic materials in the diet. Carbohydrate is 100 per cent, protein 58 per cent, and fat 10 per cent glycogenic. Glycogenic materials, furthermore, are converted to pyruvic acid before they are oxidized. In 1946 Godlowski (14) suggested a defect in the enzymatic oxidation of pyruvic acid as a cause of obesity.

Evidence has been presented for a defect in the oxidation of pyruvic acid as a cause of obesity (15) and a treatment based on this principle has been described (16). The recommended diet is a calorically unrestricted one, very low in carbohydrate, high in fat and moderate in protein. Neither fat nor protein is restricted, however. Identification of the precise step at which the defect in the oxidation of pyruvic acid occurs has had to await a detailed knowledge of pyruvic acid metabolism. Progress in this area of biochemistry has been very rapid during the past few years and, although some details have not yet been completely clarified, sufficient has been learned to exclude the more grossly erroneous suggestions and to indicate the direction in which the answer is most likely to be found.

Intermediary Metabolism of Carbohydrate and Fat

In Figure 1, reactions 1, 2 and 3 trace the series of changes that occur in glucose during the course of its breakdown to the 2-carbon substance, acetyl coenzyme A (Co A), which then follows reaction 4 as it enters the Krebs cycle for final oxidation to carbon dioxide. Reactions 5 and 6 trace the course of fatty acids in their breakdown to acetyl coenzyme A which, like the same substance formed from glucose, follows the path of reaction 4 into the Krebs cycle. Reaction 1, actually, includes a whole series of events—the glycolytic phase of carbohydrate breakdown—resulting in pyruvic acid. Neither it nor the Krebs cycle is given in detail here for they are relatively well known; they have recently been presented in an excellent review (17).

One of the notable achievements of biochemistry in the past few years has been the discovery that many of the intermediate products of metabolism are not

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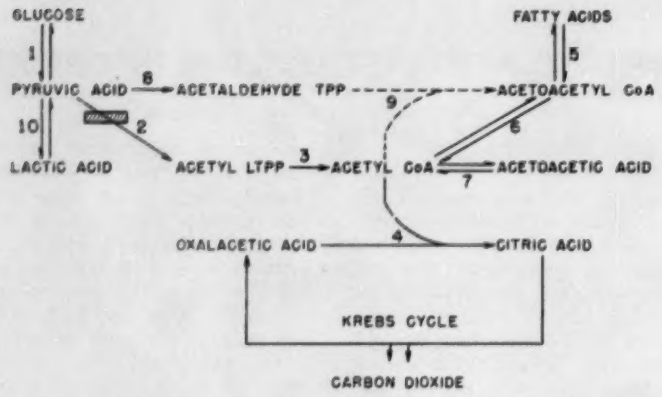

Figure 1: Metabolic interrelations of carbohydrate and fat. (Lactic acid, formed in reaction 10, does not lie in the main pathway of carbohydrate breakdown but can only be reconverted to pyruvic acid.)

free substances but are joined to coenzymes, which affect their reaction characteristics in very significant ways. (The enzymes with which the coenzymes cooperate are large protein molecules of unknown structure, but the chemical structures of most of the coenzymes are known. The general role of vitamins in the body is to serve in the structure of coenzymes.) In reaction 2, pyruvic acid becomes linked to the coenzyme, lipothiamide pyrophosphate (LTPP), and the product of the reaction is acetyl LTPP. This makes possible reaction 3, in which LTPP is exchanged for coenzyme A (18), resulting in acetyl CoA. The latter substance is the "active acetate" often mentioned in the literature of the recent past. Its reaction characteristics are quite different from those of free acetate (acetic acid), which it resembles except for the linkage of the "acetyl" group with coenzyme A.

In the breakdown of fat the long-chain fatty acids become linked with coenzyme A, which accompanies them as they give off 2-carbon molecules by the process of beta-oxidation (19). The 2-carbon molecules are not acetic acid; as they are given off they, too, become linked with coenzyme A, with the result that the long-chain fatty acids, in the process of shortening, give off successive molecules of acetyl coenzyme A. Reaction 5 includes a whole series of events that occur in the breakdown of the long-chain fatty acids, down to the point where only a 4-carbon molecule remains. This has become oxidized to form acetoacetyl coenzyme A, a substance that differs greatly in its reaction characteristics from its free form, acetoacetic acid (diacetic acid). This 4-carbon molecule, acetoacetyl Co A, subsequently is split, in reaction 6, to form two molecules of acetyl Co A.

Acetyl Co A is a very reactive substance. The attachment to coenzyme A affects the distribution of electrical charges within the "acetyl" group, facilitating condensation of "acetyl" with other substances. Thus, in reaction 4, it condenses with oxalacetic acid to form citric acid. In reaction 7 it condenses with another molecule of its own kind to form free acetoacetic acid (diacetic acid). This occurs primarily in the liver; the acetoacetic acid is then carried through the blood stream to the general tissues, where it is reconverted to acetyl CoA and oxidized through the Krebs cycle. Acetyl CoA supplies most of the energy needed by the brain and nervous system and by all of the tissues of the body. Acetyl CoA enters into a number of acetylating reactions with other substances. Also, since the series of reactions 5 and 6 is reversible, it can be rebuilt into fat. The various reaction paths of acetyl CoA provide a field of competition among the substances with which it is able to combine; in addition, hormonal and other factors appear to influence the direction of the metabolic pathways.

Fat can be formed, as the diagram shows, from any substance that breaks down to form acetyl CoA. This includes not only fat itself, but carbohydrate and also protein. The metabolic pathways of protein are omitted for simplicity, but after protein becomes deaminized it can enter the Krebs cycle for oxidation, much of it by way of pyruvic acid and acetyl CoA.

While it has been found that coenzyme A is definitely involved in the synthesis of fat, there is strong evidence that fat formation in the body can not be explained entirely by a simple reversal of reactions 5 and 6. Fat is built up from active 2-carbon molecules, but acetyl CoA is only one of three forms in which active 2-carbon molecules occur. Acetyl LTPP, the product of reaction 2, is one of these. Another is acetaldehyde thiamine pyrophosphate (TPP), formed in reaction 8 from pyruvic acid. In the breakdown of pyruvic acid there is competition between coenzymes TPP and LTPP for linkage with it. The latter coenzyme, according to Reed and De Busk (20), must first be constructed by conjugation of lipoic acid with thiamine pyrophosphate, and these investigators have isolated an enzyme, lipoic acid conjugase, that negotiates this preliminary step. When the specific enzyme is lacking pyruvic acid can not proceed by way of reactions 2 and 3 to form acetyl CoA, for the necessary coenzyme, LTPP, can not be formed. Other metabolic pathways of pyruvic acid remain open, however; pyruvic acid can still undergo reaction 8 to form acetaldehyde TPP. Ordinarily, pathways 2 and 8 are both open; both acetyl LTPP and acetaldehyde TPP are formed in greater or less amounts.

Acetaldehyde TPP is a very reactive substance, entering readily into transketolating and synthesizing

reactions to form longer carbon-chain compounds (acetoin, acyloins). There is circumstantial evidence that acetaldehyde TPP is an active 2-carbon unit in the synthesis of fat, and the dotted lines of reaction 9 suggest one way in which it might participate. In this hypothetical reaction, a molecule of acetaldehyde TPP combines with a molecule of acetyl CoA, possibly with the formation of intermediate compounds, to form a molecule of acetoacetyl CoA; additional molecules of acetaldehyde TPP are added later, lengthening the fatty acid chain. This would constitute a sort of "metabolic bridge" between carbohydrate and fat, making possible a synthesis of fat from carbohydrate by way of reactions 1, 8, 9 and 5, as well as by reactions 1, 2, 3, 6 and 5.

The evidence for a metabolic bridge of this sort is derived from a variety of sources. The formation of fat from carbohydrate by means of some form of aldol condensation was, for many years, held as a most reasonable mechanism, but it encountered the difficulty that no acetaldehyde could be found. This difficulty no longer exists, for acetaldehyde is known to occur in the normal process of metabolism, not in the free state of course, but linked to the coenzyme, thiamine pyrophosphate. Thiamine, furthermore, appears to be involved in the conversion of carbohydrate to fat; the ingestion of large amounts of thiamine in conjunction with a high carbohydrate diet causes a fatty liver (21).

Part of the evidence for such a "metabolic bridge" is derived from experiments in which free acetate (acetic acid) is injected into the organism. Free acetate does not occur in the normal processes of metabolism, but when it is injected it readily reacts to form active 2-carbon molecules, which then can be oxidized or built into fat. Free acetate readily reacts with coenzyme A to form acetyl Co A, which then can follow any of the metabolic pathways of this substance. It has been found, however, that free acetate forms fat more readily than does acetyl Co A (22) and, furthermore, that injected acetaldehyde forms fat more readily than does free acetate (23). This would seem to indicate that when acetate is injected the part of it which engages most actively in fat formation is diverted to some other pathway and forms some active 2-carbon unit other than acetyl Co A. In its progress toward fat formation it would seem to follow a pathway to acetaldehyde or the active form of this, acetaldehyde TPP. Acetaldehyde TPP is readily converted to free acetate in the presence of suitable electron acceptors (18), and the reverse should readily take place in the presence of one of the electron donors that exist abundantly in the organism.

For the formation of fat it has been found that glycolysis (reaction 1) is necessary. An explanation that has been suggested for this is that the energy released in glycolysis is needed for fat synthesis. During fasting and other states in which glycolysis is in abeyance, however, much energy is made available by the oxidation of fat through the Krebs cycle, and although this energy can be utilized in condensing acetyl Co A, through acetoacetate, to synthesize cholesterol, the organism is unable to utilize it for the formation of fatty acids. This caused Brady and Gurin to suspect a route for fat synthesis alternative to that of simple reversal of reactions 5 and 6 (24) (25). It appeared that the 2-carbon units engaging in fat synthesis must be drawn from a metabolic pool different from those entering the Krebs cycle for oxidation.

Whether or not the metabolic bridge presented here proves to be the one in actual operation, there is other evidence that carbohydrate can be converted to fat without first breaking down to acetyl Co A. Hift and Mahler (26) have discovered an enzyme that joins pyruvic acid to one-carbon molecules, to form a 4-carbon fatty acid derivative. Also, glycogen is readily converted to fat in the adipose tissues and, although this is believed to occur by way of pyruvic acid, there is no evidence of the formation in these tissues of any abundance of the readily oxidizable acetyl Co A.

FAT METABOLISM IN OBESITY

Studies by Mayer on genetically obese mice (27) show that injected pyruvic acid and injected acetate both tend to accumulate in the tissues, and he has postulated, as the primary metabolic fault in this form of obesity, an impairment in the ability to oxidize acetate. Acetate, however, is not formed in the course of the metabolic breakdown of any food substance; when injected it is metabolized only after it has reacted in the tissues to assume an active form. Since the obese mice were able to oxidize fat and to lose weight on a protein-fat diet (28) it seems clear that the pathways of fat breakdown, including the entrance of acetyl Co A into the Krebs cycle (reaction 4), were open. The metabolic fault in this form of obesity, therefore, must lie at a point above the level of acetyl Co A; it must be looked for somewhere between pyruvic acid and acetyl Co A (reactions 2 and 3). Reaction 2 is a vulnerable one, as Reed and DeBusk have shown in certain lower organisms (20); the vulnerability consists in an easily impaired ability to form the coenzyme LTPP that is necessary to convert pyruvic acid to acetyl Co A. The formation of the coenzyme, LTPP, depends on the ability to conjugate lipoic acid with thiamine pyrophosphate, and the activity of the enzyme, lipoic acid conjugase, required to accomplish this, appears to be impaired with relative ease. There seems reason to suspect, therefore, that one cause of obesity may be pin-pointed as a lack of, or impaired activity of, the single enzyme, lipoic acid conjugase. The shaded block in reaction 2 indicates the metabolic pathway that would be obstructed or impaired by this defect. Pyruvic acid would tend to accumulate in the tissues, and more than a usual amount of it would be diverted toward fat formation.

The development of obesity in the presence of such a defect could not be explained without reference to the work that Wertheimer and others (29) have done on the hormone-like quality that the products of metabolism, themselves, exert upon the direction of metabolic pathways. Pyruvic acid, significantly, checks the formation of free acetoacetic acid in the liver (30), checks the breakdown of fat and directs the metabolic pathways toward fat synthesis (31). Various explanations have been suggested for these actions but, whichever is the correct one, it can easily be seen that the effects of an accumulation of pyruvic acid would lead to obesity. Pyruvic acid also inhibits the oxidation of free acetate, causing this substance to accumulate when it is injected into the organism (32).

INTERMEDIARY METABOLISM IN TREATMENT

The explanation given here would seem to show why it is that high fat diets are more efficient than high carbohydrate diets in weight reduction. Restriction of carbohydrate reduces the amount of pyruvic acid formed, so that a block in reaction 2 would no longer have the effect of causing excessive amounts of pyruvic acid to accumulate. Inhibition on acetoacetic acid formation and on fatty acid breakdown would be lessened, and less pyruvic acid would be diverted to the formation of acetaldehyde TPP through reaction 8. By a change from carbohydrate to fat in the diet, the effects of a block in reaction 2 would be circumvented.

Many diets for obesity have restricted carbohydrate. The effective low calorie diets of Strang and Evans contained only 40 grams of carbohydrate (33). The diets of Ebstein (34) and Germain See (35) restricted carbohydrate severely while allowing more liberal amounts of fat. The recent diets of Ohlson (6) and Young (11) have followed this principle to some extent. Ebstein and Germain See went so far as to restrict protein also, on the ground that it, like carbohydrate, stimulated fat formation; the breakdown of 58 per cent of protein through pyruvic acid would seem to provide a rational basis for this. A high protein diet, however, has so many proved merits aside from the question of weight reduction that restriction of protein would seem inadvisable; protein may help weight reduction in the long run by its effect in gradually increasing the basal metabolism (36).

In the clinical practice of medicine one encounters obese people who have reduced their weight simply by avoiding the more concentrated carbohydrate foods. From their point of view they have merely been "restricting calories," but they have, nevertheless, been limiting the amount of pyruvic acid formed in their tissues. In many cases this appears to be all that is necessary to adjust the weight to normal; apparently the obesity defect exists in these individuals only to a mild degree. Such patients, however, are likely to become hungry if they do not increase their fat intake. Only 10 per cent of fat (the glycerol fraction) is metabolized by way of pyruvic acid, and this would seem to make fat the source of energy, par excellence, for people with a tendency to obesity. Provided carbohydrate is restricted sufficiently, there does not seem to be any need to restrict fat at all. Other cases of obesity appear to have an obesity defect that is much more severe. With them, it appears necessary to restrict carbohydrate to a rigorous degree; this is highly preferable to restricting protein which, though it forms pyruvic acid, does so to a lesser extent than carbohydrate. Still, there seems no need for them to restrict dietary fat; the total caloric intake, in the absence of interfering factors, adjusts itself to the energy needs of the individual. Although the emphasis has often been put on protein in constructing diets for the obese, it seems that the emphasis should be put on fat as the major source of energy, with carbohydrate restricted to the degree necessitated by the obesity defect, and ample protein allowed for its well-recognized benefits to health.

SUMMARY

Controlled experiments on the relative efficiency of carbohydrate, fat and protein in weight reduction diets indicate that obese people lose more weight when most of the calories are derived from fat. These findings are explained by a concept of obesity as due to an impairment in the oxidative pathway of pyruvic acid. Recent advances in the biochemistry of pyruvic acid are reviewed and an attempt is made to identify the precise point at which the metabolic defect occurs. Implications in treatment are mentioned.

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CLINICAL EXPERIENCES WITH FOUR NEW ANTISPASMODIC SUBSTANCES

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THE SEARCH for improved chemical compounds which should decrease gastric acidity and motility in patients with peptic ulcer has been going on for many years. Investigators produced a number of compounds which were analogous to atropine but which clinically failed because they improved so little on atropine (1). The search received however, an additional stimulus when tetraethylammonium was introduced into clinical medicine and was shown to possess remarkable effect on gastric secretion and motility (2).

A series of new compounds was then prepared which were combinations of tetraethylammonium and other substances (3).

Tetraethylammonium, a substance structurally related to acetylcholine, has the capacity to block the transmission of both sympathetic and parasympathetic nerve impulses at the autonomic ganglia (4). It inhibits gastric secretion and motility in man; it reduces the amount of nocturnal secretion (5); it decreases the secretory response to alcohol, histamine and insulin in patients with peptic ulcer (6). However, it has to be given parenterally; its action is temporary and it produces more or less severe side effects—e.g. postural hypotension, tachycardia, faintness, weakness, blurring of vision, numbness, tingling, dryness of mouth, etc.—which have prevented it from becoming widely used therapeutically (7).

Since its introduction many similar chemical compounds have been developed with the hope of finding a therapeutic agent with sufficient parasympathetic blocking action to reduce gastric motility and secretion but which could be used orally and which would have none or fewer of the above mentioned side effects.

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Most of the chemical compounds thus produced have been substances representing the combination of an amino-alcohol ester structure with the quaternary ammonium structure of tetraethylammonium. These substances are more or less effective orally and seem to have sufficient selective parasympatholytic action to decrease gastric secretion and motility without producing too many side effects (8).

Banthine was the first of these chemical compounds to be marketed and enjoyed a great popularity after its introduction some ten years ago (9). After some time however, during which it received a wide clinical trial, its undesirable side effects— dryness of the mouth, mydriasis, cycloplegia, constipation, and urinary retention (10)—suggested the need of other compounds which would be better tolerated.

Many investigators have been working on this problem and have come up with a large number of newer cholinergic blocking agents of slightly different chemical structures, which seem not only to be more effective in regard to gastric secretion and motility but which also have even less side effects (11).

In this paper we wish to discuss briefly our experiences with four of these newer compounds—*Probanthine, Antrenyl, Monodral* and *JB 323* (*Piptal*) concerning their effect on gastric acidity and on clinical symptoms.

The clinical effects were studied on patients presenting a variety of complaints concerning their digestive tract and who fell into the following categories: duodenal or gastric ulcer, hypertrophic gastritis, pylorospasm, irritable bowel, ulcerative colitis and biliary tract disease (chronic cholecystitis, postcholecystectomy syndrome ((biliary dyskinesia)) and chronic pancreatitis.

These substances were given to ulcer patients in addition to a diet, sedatives and antacids. In the gastritis or bowel case it was given only in association

with a sedative and an appropriate diet. Some of these patients had been previously on either belladonna or atropine or some other antispasmodic with only moderate or insufficient relief.

The secretory studies were performed only on patients having duodenal or gastric ulcer or hypertrophic gastritis.

The hospital patients who were put on this regime were interviewed daily during the hospital rounds as to their symptoms. The outpatients from the gastrointestinal clinic or in private practice who received these substances were seen first at weekly and later when their symptoms had improved at bi-weekly intervals during which time they were questioned about their symptoms. Besides interrogating the patients for their symptoms they were also asked as to how this medication agreed with them. (Actually there was no interrogation for symptoms. The patients were only asked how they felt and they were the ones who would then mention the type of symptoms they were having or if they had no symptoms. They would also volunteer as to any untoward effects from the drug itself). Some patients were kept on the medication from 2 to 4 weeks. Others took it for a much longer period, several patients having taken the medication for three months and over in accordance with our policy to give patients with ulcers antispasmodics and antacids for several months.

If no relief of symptoms had occurred within one week, the particular test substance was discontinued and replaced with another test substance. Similarly if untoward symptoms had occurred with any one of the test substances this particular drug was also discontinued. Slight dryness of the mouth, metallic taste, mild heartburn, etc., were considered as minor side effects and ignored. Severe dryness of the mouth and urinary retention were believed sufficient indication for discontinuation of the particular test substance.

A total of 132 test cases were thus studied. Of these 64 were men and 28 women. The oldest patient was 70 and the youngest patient 17 with an average of 46 years. 56 patients were ulcer cases (6 gastric and 50 duodenal) while the remainder were patients suffering from various other types of diseases of the alimentary tract (colitis, gall bladder disease, spastic colon, etc.).

GASTRIC SECRETORY STUDY

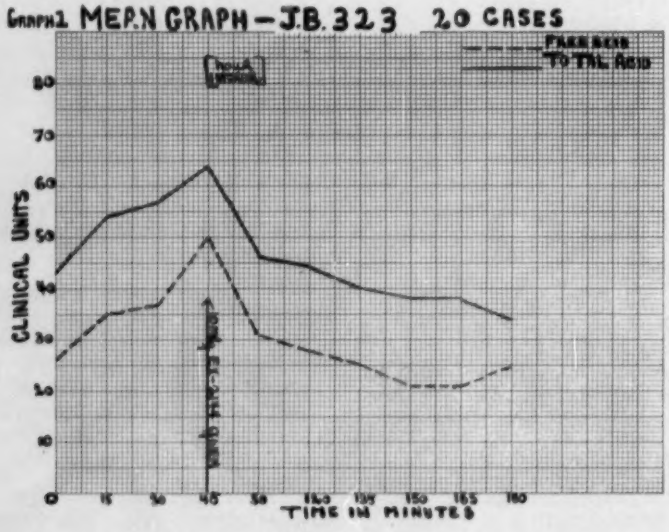
Patients with duodenal or gastric ulcer or with hypertrophic gastritis were fasted for 12 hours. The following morning they were intubated and 4 specimens of gastric juice aspirated at 15 minute intervals. The free and total acidity was determined in each of the specimens, and the results served as the base line for the control period. Following the fourth aspiration the patient was given orally an equivalent dose of the particular test substance with a few c.c. of water. One hour after the administration of the test substance, the patient was again aspirated and the aspirations were repeated at 15 minute intervals for 90 minutes. Determination of free and total acidity was done and the results compared with those of the control period.

The following substances were tested: Monodral (2-Diethylaminoethyl 2-cyclopentyl-2-(2-thienyl) hydroxyacetate methobromide), Antrenyl (Diethyl (2-hydroxyethyl) methylammonium bromide a-phemylcyclohexane-glycolate), Probanthine (B-di-isopropylaminoethyl xanthene-9-carboxylate methobromide) and JB 323 (Piptal) N-Ethyl-3-piperidyl benzilate methobromide).

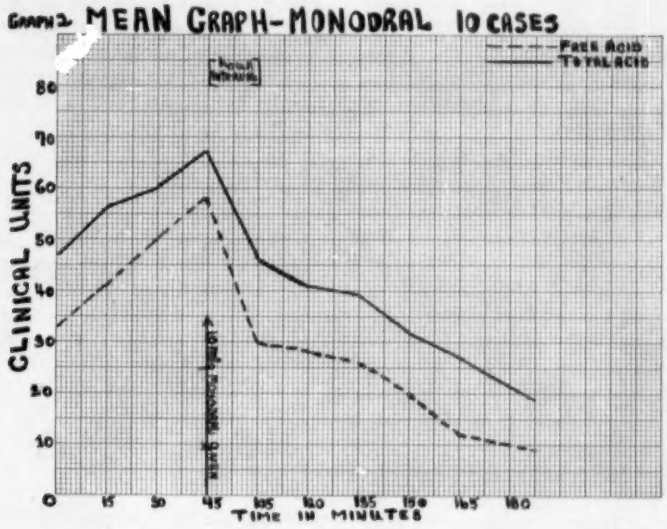
RESULTS

A. Clinical

JB 323 (Piptal) was given to 52 patients in doses of 5 mg. every 6 hours. The majority of the patients experienced relief of some of their symptoms after the first couple of doses (2-4) with a gradual decrease in the number and severity of the symptoms with the continuous use of the medication. As the symptoms (cramps, gas, tight feeling, nausea, and epigastric distress) disappeared the medication was stopped after 2-4 weeks on most of the irritable bowel cases but was



Graph 1



Graph 2

continued in the ulcer patients. In some patients the medication was restarted if symptoms reappeared after a while.

Monodral was given to 45 patients. 34 patients received 5 mg. every 6-8 hours and 11 patients received 2 mg. every 6 hours.

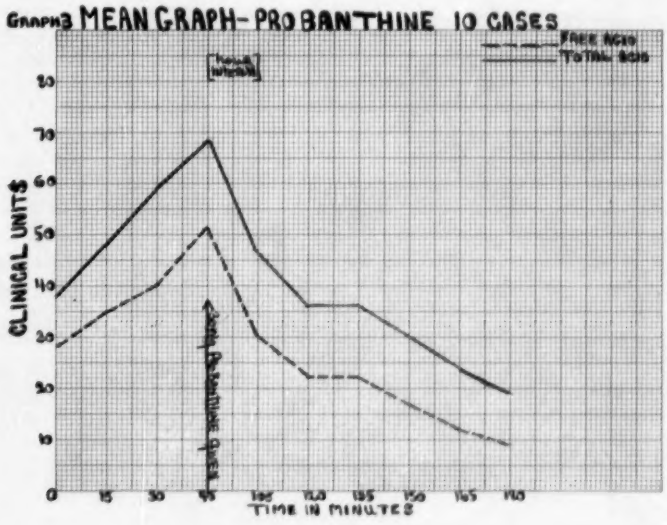
The subjective symptoms were relieved in most of the patients after the first few doses as after JB 323 (Piptal).

Probanthine was given to 23 patients in doses of 15 mg. every 6 hours. The clinical results were much like those following JB 323 (Piptal) and Monodral.

Antrenyl was given to 12 patients. This substance gave clinical results somewhat similar but less promptly and to a lesser degree than those obtained with JB 323 (Piptal) and Monodral.

UNTOWARD EFFECTS

Most of the patients stated that they had at one time or another a slight dryness in the mouth following 5 mg. of JB 323 (Piptal) every 6 hours. A few who had more marked dryness had to be restricted to one capsule every 8 hours and this relieved the dryness. In no instance did we have to stop the medication because of dryness or because of any other untoward side effects. It is to be noted particularly that in no instance did any patient complain of urinary disturbances as has been occasionally noted in other patients who were taking other similar substances.



Graph 3

Monodral too was well tolerated except for moderate dryness of the mouth in about 25 per cent of the cases especially with the larger dose. Mild dryness was noted by almost all patients. One patient had a metallic taste in her mouth, two had a sensation of heart burn and in one the urinary bladder became distended.

Except for slight dryness in a few patients Probanthine too was well tolerated. Two patients of this group however, had a mild urinary retention. Of the 12 patients taking Antrenyl about half complained of mild dryness and one developed a mild urinary retention.

B. Secretory Study Results

Following 10 mg. of JB 323 (Piptal) given orally there was a definite decrease in the acidity curve 1 hour after ingestion of the substance. The decrease continued for 1½ hours (as long as the observation was continued). (Graph 1). The acidity dropped within 75 minutes after the ingestion of 10 mg. of Monodral. The mean curve showed a continuous drop of the acidity (both total and free) during the time of observation 2½ hours. (Graph 2) In some of the patients thus tested an anacidity for short periods (15-45 minutes) was obtained, although the mean curve does not show this. In one patient the acidity seemed to show a tendency toward rising again 2 hours after the intake of this medication.

The mean secretory results following 30 mg. of Probanthine were similar to those obtained with Monodral (Graph 3).

The secretory results following 10 mg. of Antrenyl seemed to show more depression of the mean acidity curve than after the other substances (Graph 4).

DISCUSSION

Our studies indicate that all 4 substances tested had good clinical results in that they relieved the patients' symptoms. While it seemed that Monodral and JB 323 (Piptal) were preferred by some patients to Probanthine and Antrenyl, this may have been only an apparent preference since a larger number of patients had Monodral and JB 323 (Piptal) than Probanthine and Antrenyl. It is also possible that because of the somewhat more drying effect produced by Antrenyl and Probanthine the patients developed an antagonistic feeling towards these substances and therefore may have been somewhat negativistic during the interview concerning their subjective symptoms. One must also consider the fact that because of the smaller number of patients tested with Probanthine and Antrenyl the percentage of side effects is comparatively higher than if a larger sample were studied. In support of the above assumption, it can be noted that the graphs showing the results of the antisecretory studies show comparatively little variation in the degree of acidity decrease. Moreover in our cases Antrenyl, which had only a fair clinical response, gave apparently the lowest acidity curve.

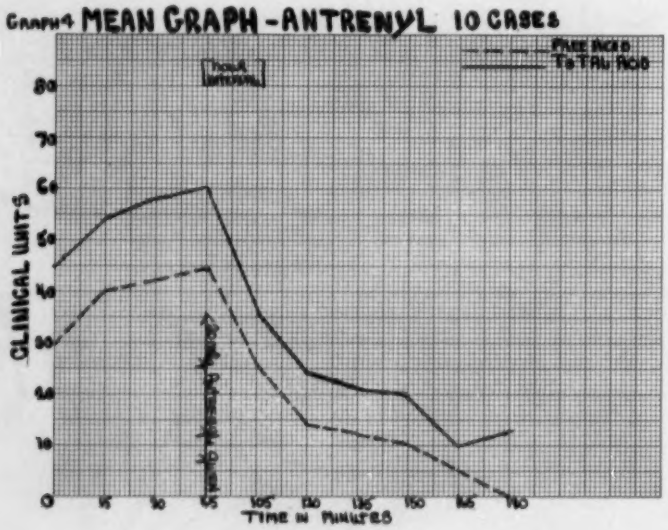
These observations (clinical and secretory) seem to indicate that any one of these four substances is comparatively well tolerated by the average patient who needs such therapy. The benefit which the patient obtains from either of these substances does not depend merely on the amount of antisecretory activity, but may depend also on the degree of decrease in motility (12), number and severity of side effects and purely individual characteristics such as reaction to the taste, color, appearance and other physical properties of the medication.

SUMMARY

Four of the newer anticholinergic substances were tested concerning their clinical and antisecretory effect.

All of them gave good clinical results as judged by the patient's subjective symptoms. They also had almost equal effects on gastric acidity.

In this group, side effects occurred most frequently



Graph 4

with Antrenyl and infrequently with JB 323 (Piptal) in the decreasing order Antrenyl, Probanthine, Monodral, JB 323 (Piptal). JB 323 (Piptal) was the only substance in this study which had no urinary side effects.

The clinical results of these anticholinergic substances seem to depend on other factors besides their antisecretory effect.

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THE USE OF CITRUS FLAVONOIDS IN INFECTIONS. II.

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THAT DISTURBANCES of capillary function accompany the inflammatory process, has long been known. The physiologic and morphologic changes in the vessels that accompany this phenomenon were described in Krogh's classic Silliman lectures (9) of 1922:

"In inflammation the circulatory phenomena are generally very conspicuous and by a large school of pathologists they are regarded as the primary and essential symptoms to which all others can and should be referred. . . . In my opinion, the vascular reactions in typical inflammation are, in the main, of a secondary character, though . . . they form, nevertheless, an element of prime importance in the complicated inflammatory processes. . . .

"It may very well be worth while to study the vascular reactions during inflammation with the object in view of getting them under control, of restraining them at the points

where they become harmful and of helping them on where they are beneficial."

In inflammatory reactions caused by infection, there is invariably involvement of the capillary circulation. The changes that occur in the capillaries at the site of inflammatory lesions were never better described than in some of the older textbooks of physiology (e.g., 21) and pathology (e.g., 7). Briefly, there is first dilatation of the vessels, with increased blood flow, followed by a slowing of the axial stream and collection of leukocytes along the capillary wall; the leukocytes may then emigrate through the wall by diapedesis. There is simultaneously transudation of protein-containing fluid through the capillary wall, with production of localized edema, and, in some infections, rupture of the capillary intercellular cement occurs with release of erythrocytes, producing "hemorrhagic inflammation." This phenomenon is not restricted to bacterial infections, nor even to the site of invasion of the infective agent. Sokoloff (16) has recently reviewed changes in capillary permeability and fragility which are known to take place in many viral infections and which often are not restricted to sites of invasion or localization, but occur throughout the body.

In a preliminary note (5), we have reported our initial findings on the remarkable ameliorative effects of the water-soluble citrus bioflavonoid complex in acute respiratory infections. Rhinitis, pharyngitis, influenza, tonsillitis and the like usually subsided completely in from 8 to 48 hours. Further observations confirm these findings and indicate that the beneficial effects of the flavonoids are not confined to respiratory infections or solely to viral diseases. Our results strongly suggested that the flavonoids operate in the infections, at least in part, by restoring normal capillary integrity, a function of this group of compounds originally demonstrated by Armentano, Szent-Györgyi and their associates (1) in 1936. While our own observations were entirely empirical in basis, Krogh's suggestion of more than thirty years ago has proved to be a valuable one indeed.

In addition to the 23 cases of respiratory infections treated with citrus flavonoids, which were the subject of our preliminary report, we have investigated the effects of flavonoid therapy* in an additional 46 cases, or a total of 69. Our subsequent observations have fully confirmed our conclusion that these substances are of inestimable value in the treatment of certain infections. In addition to our series of cases, Sokoloff (16) has reported five cases of influenza, verified as caused by influenza virus A, in which recovery occurred by crisis within 48 hours, under large dosage therapy with the citrus flavonoids.

Following are brief additional descriptions of typical cases:

*The preparation used in this study was C.V.P.®, a mixture of equal parts of whole water soluble natural citrus flavonoid complex, and ascorbic acid. These citrus flavonoids, similar to, but not identical with, the original preparation of Szent-Györgyi, which he designated vitamin "P", have been described by Sokoloff, Eddy and Redd (17). The commercial preparation, kindly supplied by the U. S. Vitamin Corporation, contains in each capsule 100 mg. each of flavonoids and ascorbic acid. Throughout this paper, except when otherwise specifically stated, dosage refers to the flavonoid component (100 mg.=1 capsule).

A woman, age 49, developed an acute membranous tonsillitis and pharyngitis, with a temperature of 101 F. She was given 200 mg. of flavonoids every 3 hours (1.8 Gm. per day). In 48 hours the temperature was normal, injection and swelling were gone and the membranous coatings were found to be peeling off without bleeding and with normal appearing mucosa underneath. The patient could now swallow without discomfort and had little residual malaise (after a total dosage in 48 hours of 3.2 Gm.).

Another patient, age 55, a telephone operator, was seen 48 hours after development of a severe rhinitis. There was no fever. This patient had a history of almost invariable chest involvement following previous attacks of rhinitis and subsequent development of asthma. On several occasions the latter required hospitalization for 2 to 3 weeks. She was given 200 mg. of flavonoids 3 times a day and was completely free of symptoms in 36 hours. In contrast to previous experience, the patient was able to continue at her work. As she expressed it, "For the first time in my life the cold cleared up like magic."

In another patient, female, age 43, with acute laryngitis and pharyngitis, there was complete subsidence of symptoms in less than 72 hours on a flavonoid dosage of 200 mg. 3 times a day.

A woman, age 48, developed influenza while taking soluble citrus flavonoids 200 mg. per day, as a maintenance dose against increased capillary fragility. She had pharyngitis, rhinitis, sinusitis, severe malaise and a temperature of 99.7 F. The flavonoid dosage was increased to 800 mg. per day (2 capsules 4 times a day). Two hours after the first dose of 200 mg. there was noticeable thickening of nasal mucus. The temperature was normal in 14 hours (after 600 mg.) and all signs and symptoms, local and systemic, had subsided except for persistence of some thickened mucus in the nasal passages. There was a marked sense of relief and well-being the next day, on which the patient remarked spontaneously. Flavonoid therapy was continued, 600 mg. a day, for another week, until nasal secretions were normal. Previous experience of this patient with respiratory infections was that while they occurred rarely, when they did the course was extremely severe and residual symptoms were very persistent, lasting usually for several weeks. An interesting observation in this case is that a long-standing rheumatoid arthritis of the hip cleared up completely during the flavonoid therapy (this response to flavonoids in certain cases has been reported by Sokoloff and Eddy (18)).

A male diabetic, age 41, developed rhinitis while taking 600 mg. of flavonoids per day for therapy of retinitis. The same dosage was continued; in contrast to his usual experience, there was rapid thickening of nasal mucus and this infection lasted only 3 days and was mild in character. Respiratory infections in this patient had previously invariably lasted considerably longer and were usually severe.

A man, age 43, developed a severe rhinitis with copious watery secretion. On a dosage of 600 mg. of flavonoids the first day, and 900 mg. per day on the two following days, there was complete subsidence of all symptoms in approximately 52 hours. In this case,

excess nasal secretion subsided without going through the phase of thickening. There were no residual complications although previous experience of this patient had been that attacks of rhinitis were invariably followed by persistent frontal sinusitis.

In a few patients discontinuance of therapy as soon as the respiratory symptoms subsided was followed by recrudescence of the infection which, however, again responded to flavonoid therapy. It seems advisable therefore to continue flavonoid therapy for at least a few days after the infection has subsided, and especially when minor signs, such as thickened mucus, persist.

While the large majority of patients thus far studied have responded dramatically to the flavonoids, in three of our more recent cases, all severe respiratory infections with bronchial involvement, the flavonoids failed to arrest the infection in the usual time, but appeared to modify considerably the course of the infection as compared to previous similar attacks in the same patients. In the case of a man, age 48, who had been accustomed to a yearly bout of influenza for more than ten years, fever had usually risen to 101.5 F. for three or four days, and after subsidence of the infection there had always been asthenia and persistent cough for from two to four or five weeks. In his current attack, flavonoid therapy, 200 mg. 4 times a day, was administered; the temperature rose only to 99.5 F. and was normal in 24 hours; rhinitis subsided completely in 5 days and the cough had disappeared in 10 days. There was noticeably less asthenia than in previous attacks. In this patient too, as in one of those previously mentioned, a long-standing arthritis of one shoulder cleared up almost completely, leaving no pain and only slight limitation of motion. About two months later, this patient again developed a severe rhinitis with copious watery secretion. Two doses of flavonoids, 200 mg. each, were administered during the late afternoon and evening. By morning nasal mucus was extremely thick and breathing was difficult. With a single additional dose of 200 mg., the thickened mucus had almost disappeared an hour later, and about 20 hours after the initial symptoms began, the attack had subsided completely.

In our subsequent experience, in only one further case (in addition to the two failures previously reported) was there an apparent failure of flavonoid therapy. This was in a severe respiratory infection with bronchial involvement. The patient discontinued therapy after three days when the infection did not subside. There is no way of estimating in this case whether or not the flavonoids modified the course of the infection.

Trial of the flavonoid preparation in acute bursitis has led, in the few cases we have so far investigated, to such rapid and complete relief as to warrant mentioning this experience also. One case is illustrative: A man, age 38, had severe subpatellar bursitis. There was extensive local swelling, local heat, extreme tenderness, severe pain and limitation of motion. On flavonoids 200 mg. 3 times a day, there was noticeable diminution in swelling and pain in 24 hours, and in 72 hours the lesion had subsided almost completely, leaving only slight local tenderness.

DOSAGE

The dosages of the flavonoid-ascorbic acid mixture we have used in the infections have varied from 3 to 16 capsules (300 mg. to 1.6 Gm. each of flavonoids and ascorbic acid) a day, in divided doses. Optimum dosage has not as yet been worked out, but at present our dosage range is usually from 6 to 12 capsules a day, depending on the severity of the infection. Except for occasional central nervous system stimulation (and rare insomnia) on the higher amounts, which subside immediately on reduction of dosage, no ill effects have been observed. Sokoloff (16) has used even higher dosages (up to 24 capsules in 24 hours) in influenza, without apparent ill effect.

DISCUSSION

In our preliminary report, as already noted, we suggested that the flavonoid preparation operates in the infections by restoring normal capillary permeability. It is presumed that this aids recovery by preventing further penetration through the capillary wall of the large molecular proteins (6, 20), making up the attacking virus, or of other large molecular aggregates, such as bacterial polysaccharides.** It is well known that in early stages of increased capillary permeability, large molecules, normally retained, may penetrate through the capillary wall. And it has been demonstrated that this can be prevented by the administration of the citrus flavonoids (17-19). Menkin has isolated a substance from inflammatory tissue ("leukotaxine"), that damages the capillary wall. In animal experiments, Sokoloff and Eddy (18) have demonstrated that the citrus flavonoids can prevent the capillary damage produced by Menkin's leukotaxine, and that produced by bacterial polysaccharides. They have also shown that the soluble citrus flavonoid complex is much more effective in this respect, on an equal weight basis, than the insoluble flavonoids, such as rutin and hesperidin.

It appears therefore that in infections, a vicious cycle of capillary damage may be induced. Initially increased capillary permeability, from lack of suitable local tissue nutrition, from anoxia, or from chemical or physical damage, may permit penetration of large molecular infective agents or their growth products through the capillary wall. The infective agents, or their products, further increase capillary permeability,

**It should be kept in mind that certain relatively small molecular toxic chemical compounds may undoubtedly penetrate capillaries of normal permeability. This is especially important in view of the pervasive exposure to the chlorinated cyclic hydrocarbons (DDT, lindane, chlordane, and the like) which can induce chemical rhinitis, pharyngitis and interstitial pneumonitis with mononuclear infiltration. It is important that these conditions be differentiated from actual infections (4). Similarly, the organic phosphorus insecticides (e.g., parathion, TEPP, malathion) can induce copious rhinorrhea, through inhibition of cholinesterase and release of excess acetylcholine (3). These conditions can hardly be expected to respond to the flavonoids.

Reservation must also be made with regard to current concepts as to the alleged invariably infective nature of poliomyelitis (recently the subject of a monumental review by Seobey (15)), and that of many of the cases diagnosed as "virus hepatitis" (4). Obviously, however, there may nevertheless be increased capillary permeability and fragility in all these conditions, regardless of etiology, and the capillary damage should of course be treated.

and when inflammation occurs, local tissue products also take part in this process. The end result may be extensive capillary damage throughout the body, and in fact, precisely this latter phenomenon is known to occur.

Sokoloff (16) has reviewed the extensive evidence from the clinical literature showing that many viral infections are complicated by either local or widespread severe damage to the capillary walls with increased permeability and increased fragility. This has been found to occur for instance in such diverse conditions as poliomyelitis, infectious hepatitis, rheumatoid arthritis, measles, yellow fever, the common cold, influenza, smallpox, encephalomyelitis, mumps and rabies. Thus not only does the "capillary syndrome" provide a theoretical basis for better understanding and further investigation of the processes of invasion, tissue response and resolution in a variety of infections, but recognition of the role played by changes in capillary permeability and fragility provides a new and dramatically effective means of therapy. In the common cold, for instance, it is well recognized that factors which induce local ischemia and resultant anoxia (e.g. chilling, psychogenic disturbances, etc.), impaired local nutrition, irritants and the like, all of which are known to increase capillary permeability, may enhance susceptibility to the disease.

It is of great interest that citrus juices have a long tradition of usefulness in folklore against respiratory infections. Of course, the possible dosage of soluble flavonoids in the quantities of juice usually imbibed for this purpose, must be quite small in comparison with that which we have found to be effective. Nevertheless, some persons appear to respond to dosages as low as 200 or 300 mg. of flavonoids per day, and no doubt this explains the long persistence of this tradition. Of equal interest is the fact that among the esoteric remedies employed by certain African tribes, is one "for influenza and some fevers," which consists of "an hourly dose of salted liquid from boiled red peppers" (10). As Szent-Györgyi and his associates (1) demonstrated years ago, the pepper plant is a rich source of the vitamin P flavones.

Large dosages of ascorbic acid alone have been reported also to have ameliorative effects in respiratory and other infections (8, 11). These dosages (often given parenterally) are ordinarily very much larger than that in the amounts of flavonoid-ascorbic acid mixture we have used, and in our experience have rarely given responses comparable to those reported in this paper. It is of interest that secondary effects of asorbic acid, such as hypoglycemic reactions occasionally observed, have not occurred in this series when the flavonoids were administered simultaneously. In the earliest investigations on the flavonoids, synergism between vitamins P and C on capillary permeability was observed, and it appears probable that other interactions of these vitamins also occur. Their occurrence together both in plants and in animal tissues likely reflects this phenomenon. In our preliminary report we pointed out, that although the effects on capillary permeability*** appear to be the most likely explanation of the remarkable ameliorative effects of the flavonoids in infections, the possibility of other anti-infective properties was not excluded. While preliminary observations made by us indicate that the flavonoids can reduce the severity of local bacterial infection and hasten healing in animal and man, Dr. Boris Sokoloff, in a personal communication, has informed us that the citrus flavonoids have only a slight antibiotic effect in vitro. With respect to viruses, however, a recent report by McKeen (12) provides a basis for further investigation: This observer has shown that the juice of the pepper plant (*capsicum frutescens*) greatly diminishes the infectivity of cucumber mosaic virus, ringspot virus and tobacco etch virus on a variety of plants susceptible to these infective agents. While McKeen does not indicate the nature of the active substance in pepper juice, as already mentioned this plant is rich in flavonoids. Other authors have discussed at length evidence relating to the roles of the flavonoids in plant metabolism, in detoxication, oxidation-reduction mechanisms, maintenance of normal cellular membranes and the like (18).

***The role played by changes in permeability of lymphatic vessels is a subject which also requires elucidation. The uptake of antigens and of virus particles by the lymphatic circulation and the participation of the regional lymph nodes in the resultant immune phenomena were studied ingeniously twenty years ago by McMaster and Hudack (13). In their studies the lymphatic vessels were necessarily opened at one or more points, and the extremely difficult task of assessing permeability of intact lymphatics has yet to be done.

SUMMARY

In 69 cases of acute respiratory infections (of which 23 have previously been reported), including the common cold, acute follicular tonsillitis and influenza, oral therapy with the whole water soluble citrus flavonoid complex (vitamin "P" complex) led to rapid subsidence of the infection usually in from 8 to 48 hours, occasionally somewhat longer. There were only 3 failures, and 3 further cases in which the course of the disease was apparently ameliorated but not immediately terminated. Preliminary observations suggest dramatic usefulness also in bursitis and in certain other types of infection.

The effectiveness of the flavonoids in infections is thought to be related to their ability to restore to normal impaired capillary permeability and fragility, a disturbance common to a large variety of infections.

The observations reported in this paper, assessed together with the widespread occurrence of the flavonoids in plant and animal tissues, suggest a much more fundamental role for these biologic substances than has hitherto been appreciated.

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DIARRHEAL DISEASES: A PLAN FOR THEIR PREVENTION AND CONTROL

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NO ONE complaint or group of complaints has caused so much suffering, to so many millions of people, for so many centuries, as the complaint of diarrhea. This symptom has been a constant and embarrassing companion of man in civil as well as military life. Although definite progress has been made in etiology and epidemiology, there is sufficient evidence to indicate that diarrheal diseases in general, are increasing.

Statistics on the true incidence of diarrheal disorders are lacking. The wide prevalence of these diseases may be surmised by the astounding fact that the sales of intestinal adsorbents for one year amounts to millions of dollars! About four million prescriptions for intestinal adsorbents are filled each year (1). Another fact is the unusual and increasing amount of toilet tissue used in the United States (2). For example, in 1946 four hundred thousand tons of toilet tissue were sold. In 1951 the sales increased to 588,000 tons —a staggering figure! In other words, about two and one-half rolls of toilet tissue were used on the average by each person per week. Although this figure does not represent its use exclusively for sanitation purposes, it is primarily used as a toilet tissue and gives some indication of the prevalence of all types of diarrheal disorders. Interestingly enough, this increase coincides with a corresponding rise in the number of enteric infections recorded for that period in the various Public Health reports (3).

ETIOLOGY

It is estimated that about ten percent of our population are carriers of Entamoeba histolytica (4). Diarrhea is the chief complaint of fifty percent of these carriers. An unknown percentage suffer with or harbor the other recognized intestinal pathogens, such as Giardia lamblia, Balantidium coli, shigella, staphylococci, salmonella, and other bacterial enteric infections. Add to these the viral causes, chronic ulcerative colitis and regional enteritis of undetermined etiology, psychic, allergic, glandular, neoplastic, and the diarrheas caused by heavy metals, chemicals, radiation, nutrient deficiencies, intestinal worms such as schistosoma mansoni and japonicum, strongyloides, and one will realize that an enormous number of people are involved. A conservative estimate would be about sixteen million inhabitants of our country.

Submitted Aug. 2, 1954.

FOOD SERVICE

The possibility for accidental contamination of food resulting in diarrhea has increased enormously through the years. There are about 310,000 public eating places in the United States, where approximately 53,500,000 meals are served daily to persons outside their homes (5). The consumption of sandwiches in this country has increased 215%, and salads 110%. Mass food preparation and service involve millions of foodhandlers. Among them are careless cooks, waiters and dishwashers who know little about personal or environmental hygiene. Neither are they aware of their position as important links between health and disease, carrier states and epidemics.

The supervision of so complex a structure is difficult, to say the least. Educational campaigns have been inadequate. The average layman is not suffi-

ciently informed as to where to eat, how to eat or what to eat. Knowledge of the relationship of dirty eating places and unsanitary food handling to intestinal infections must be disseminated to the public in a more effective way than heretofore.

The use of insecticidal sprays or of small doses of preservatives to retard or prevent spoilage of foods is considered harmless at present. Whether the cumulative action of these small doses is innocuous when multiplied by the number of prepared foods ingested daily by each individual still remains to be established. The remains of detergents and chemicals on cooking and eating utensils and glassware, and their effect upon the gastrointestinal tract must also be considered. The so-called "virus" diarrheal outbreaks and those of "unknown origin" of one, two or three days' duration associated with nausea and abdominal pain may ultimately fall into this category.

DIARRHEA IN INDUSTRY

Diarrhea is an important cause of absenteeism in industry. Here again accurate records are difficult to obtain. A statistical study by Devlin (6) at Frankford Arsenal where 12,000 persons are employed shows that diarrhea was the chief complaint in four percent of all non-occupational dispensary visits. Diarrheal disorders conservatively estimated add perhaps as much as 200 million dollars annually to the cost of manufactured goods in this country.

Although the symptom complex of diarrhea is conceded by all to be of extreme importance in infants and children as well as adults, any approach to its solution is met with immediate difficulties (7). These may be discussed under the headings of the patient, the family physician, the Department of Health Station, the bacteriologist and the Public Health Officer.

THE PATIENT

It is almost impossible to obtain the patient's cooperation at the onset of the illness when detection of the etiologic agent particularly in the infectious diarrheas, is most successful. He will use home remedies or over-the-counter mixtures before seeking medical aid. The patient is prone to hide the complaint because of embarrassment.

The patient must be taught that diarrhea at the onset is a beneficial reaction of the body to rid the intestinal tract of irritating or toxic contents. A stool examination at this time can lead to an early etiologic diagnosis, prevention of chronicity and save great economic losses. He must be educated to the fact that paregoric or constipating drugs offer only temporary relief. They are dangerous because they lead to retention of toxins. Absorption of these toxins causes fever, distention of the abdomen, pain, loss of appetite, nausea, vomiting and severe metabolic disturbances.

The layman or potential diarrhea patient is better informed today on cancer, tuberculosis, cerebral palsy, poliomyelitis or heart disease than the more common complaint of diarrhea. Lack of any information by the public on diarrheal diseases is the one factor responsible for the poor cooperation of these patients. In fact, the word "diarrhea" is shunned and avoided by physician and layman alike. The term "dysentery" is often substituted for esthetic reasons and regarded erroneously by the layman as a diagnosis.

Unfortunately there are no clinics in the United States exclusively for the study of diarrheal diseases (8). A patient suffering with diarrhea requires extensive and costly laboratory investigations, dietetic management, social guidance and active medical therapy. This work is highly specialized, time consuming and can be most effectively carried out only in a clinic for diarrheal diseases by a specially trained group.

THE FAMILY PHYSICIAN

The family physician must be taught that a diarrhea requires immediate etiologic investigation. However, he is usually hesitant to advise stool examinations or sigmoidoscopic studies early in the onset of a diarrhea. He may be compelled to save expense. He may succumb to the pleas of the patient for the "miracle" drugs. He may have difficulty in obtaining bacteriologic help or in contacting a specialist actually trained in this field. He therefore proceeds to treat the complaint with paregoric mixtures or anti-bacterial drugs such as the sulfonamides or antibiotics. ACTH and cortisone have also been used more recently if other therapy fails. Such treatment in cases of unclassified diarrhea is unfortunate for it masks the etiologic and clinical picture, and ultimately inhibits progress in preventive and therapeutic measures. The task of the busy family physician can be simplified by supplying him with additional and more competent laboratory facilities and by educating his potential patients to the need for greater cooperation with their private physicians.

It is the duty of every physician to examine at least one stool specimen from each of his diarrheal cases. The gross appearance and the microscopic presence or absence of pus cells and red blood cells will give him significant leads to the management of the patient. It is obviously useless to treat a non-infectious or psychogenic diarrhea with antibacterial drugs, or an infectious diarrhea with psychotherapy.

The labelling of a diarrhea as "gastroenteritis" or "food poisoning" or "dysentery" or "enteritis" by the physician before cultural studies are made have further confused this field. These terms are practically interchangeable. They do not add to our knowledge of the diarrhea. The search for the causative agent such as shigella, staphylococcus or salmonella is infinitely more valuable to the patient, his family physician, and public health official. This was well portrayed by Dauer (9) in a study of diarrheal outbreaks occurring in various units of the armed services stationed in Continental United States in 1952. Many of these outbreaks were classified merely as "food poisoning" or "gastroenteritis" although careful investigation identified the etiologic agents.

THE DEPARTMENT OF HEALTH

The local Department of Health Station or depot should be equipped with sterile, colorless, wide mouth jars for distribution to physicians or to patients on their physicians' prescription. These prescriptions should be forwarded to the Department of Health where the record of the number of bottles and demand

for them is kept. This record will serve as an indicator of the interest of the public and the family physician in the campaign presently to be described.

THE BACTERIOLOGIST

The bacteriologist or laboratory technician is an important member of the team for the new approach to this problem. He should be required to report the gross as well as the microscopic findings. The cultural studies should be done as rapidly as possible and reported promptly by mail, or when feasible by phone. A preliminary report within 24 to 48 hours might be advisable. Such a service will be rewarded by better cooperation of the physician and the patient.

The "enteric" bacteriologist or technician must have an air-conditioned laboratory or some deodorant system. The stench in most of the present day laboratories where stools are examined is almost intolerable. Good work can not be done under such conditions. Even the scientifically minded person soon loses interest in this field. At best the work involves unpleasant technical procedures. Fortunately the author's plan would obviate the need for complete stool examinations by the technician in the small hospital or average clinical laboratory.

THE PUBLIC HEALTH OFFICER

Public Health Officials are interested in diarrheal diseases from the epidemiologic point of view. This interest is therefore limited mainly to the infectious diarrheas which are reported under the general heading of "Diarrhea, Enteritis and Dysentery." A large number of cases in the non-infectious group are therefore not included. Even some of the infectious diarrheas which are self limited and of short duration are seldom reported.

The problem is further complicated in this reportable group by the fact that more than one, and frequently three or more stool specimens, must be examined in each case in order to establish a positive etiology. Hardy and Watt (10), among others, have clearly demonstrated that the number of positive findings increased from 56 to 85 percent when repeated examinations of stool specimens were made.

RECOMMENDATIONS AND IMPORTANT GAINS

In order to add to our knowledge of the true incidence of Diarrheal Diseases and to aid in its prevention and treatment, the Author recommends the following plan:

1. The Public Health Service, in conjunction with the medical profession, through its various public health committees should put into effect a campaign of educating the public in diarrheal disorders. Information on cancer, cerebral palsy, arthritis, heart disease, etc., have been successfully transmitted to millions of people through the media of the press, radio and television. Information on diarrhea must be treated in like manner.

2. The campaign should stress that a diarrhea of 24 to 48 hours' duration requires a simple procedure. This procedure would consist of sending a freshly passed stool to the nearest Department of Health Station, depot or laboratory for cytology and culture. The container would indicate the name of the patient and the name of the family physician to whom a detailed report would be mailed.

3. This procedure would lead to a chain reaction of incalculable value to the Public Health Officer. It would immediately diminish the incidence of the so-called "non-specific" diarrheas. Carriers of intestinal pathogens would be readily discovered and properly cared for. It would supply the public health departments with statistics indicating the true incidence of diarrheal disorders. The number of infectious and non-infectious diarrheas would be available for the first time in the history of the Public Health Service.

4. By educating the public further gains may be expected. It would bring the patient earlier to his family physician. Self medication would be discouraged. The delivery of the freshly passed stool after 24 or 48 hours of diarrhea would obviate the present confusion and difficulty in trying to isolate intestinal pathogenic bacteria or protozoa after barium or antibacterial drugs have been taken. Physicians would find their patients better informed and thus more cooperative.

5. The benefits to the public health service in epidemiologic data, to the individual patient in an earlier etiologic diagnosis, to the family physician in the ability to render more successful therapy, need hardly be stressed.

6. It is conceivable that as a result of this procedure a screening test for intestinal malignancies might be developed as a separate, distinct and valuable research project.

7. Experience has shown that a new medical idea reaches maturity more rapidly by educating the public first. In the final analysis it is the layman or potential patient who must be convinced of the value of this new procedure.

8. It is true that the subject of diarrhea is difficult to present to the public, but so was venereal disease only a few years ago. What is false modesty today can be scientific thought tomorrow. The objective is clear. An educational program for the public in the field of diarrheal disease is long overdue!

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ANEURYSM OF THE SPLENIC ARTERY: AN AUTOPSY STUDY*

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ANEURYSM of the splenic artery is a comparatively rare pathological condition. Most of the cases recorded in the literature were those in which surgical exploration was necessitated because of hemorrhage and rupture of the aneurysmal sac. There are less than 300 cases recorded in the literature. Up to 1952 Berger et al. reported the 152nd case. Owens and Coffey collected 190 cases up to 1953.

This presentation is based on a study of 1,319 consecutive adult autopsies in which 11 cases of splenic artery aneurysm were found. A study was also made of 114 collected clinical cases to determine certain features of this condition. The purpose of this communication is sixfold. (1) To determine the true autopsy incidence of splenic artery aneurysm. (2) To collect the recently reported cases. (3) To determine the incidence of surgical complications, such as rupture of the aneurysm. (4) To determine the site of the rupture in relation to adjacent organs and the peritoneal cavity. (5) To study the relative age in male and female cases. (6) To determine the incidence of the association of pregnancy and rupture of the aneurysm in pregnancy.

The autopsy incidence of aneurysm of the splenic artery varies from 0.039 to 0.8 per cent. The autopsy incidence varies in accordance with the thoroughness in which the examination is made, as well as making a specific search for such aneurysms. Of particular interest is Ferrari's study of 143 autopsies in subjects over 60 years of age, which revealed evidence of small minute aneurysms in 14 instances. This incidence of 9.8 per cent seems to be unusually high and may be accounted for on the basis of being of microscopic size, which are grossly not demonstrable, unless especially sought after by this method of examination. In a recent study of 1,319 consecutive adult autopsies, 11 cases of aneurysm of the splenic artery were found, an incidence of 0.8 per cent. This incidence is considerably higher than that quoted in the literature. See Table 1.

TABLE I

THE AUTOPSY INCIDENCE OF SPLENIC ARTERY ANEURYSM

Author	Autopsy cases	Aneurysm cases	Per cent
Lindboe	41,437	21	0.05
Guy	5,000	2	0.04
Garland	4,100	3	0.07
Ophüls	3,000	1	0.03
Seids and Hauser	12,894	4	0.03
Seids and Hauser (collected cases)	58,000	28	0.05
Sperling	33,810	7	0.02
Sherlock and Learmonth (collected cases)	84,000		0.039
Schroeder	32,768	20	0.06
Feldman	1,319	11	0.8

It is claimed that arteriosclerosis, hypertension and intra-abdominal pressure are the most common causes of aneurysm of the splenic artery. According to Shumway and Peyton, there seems to be a preferential sclerosis of the splenic artery to the exclusion of other abdominal vessels. On the other hand, arteriosclerosis cannot be considered the only etiologic factor, because of its frequent occurrence in young individuals, at an age when arteriosclerosis is absent or shows only a minimal degree of involvement. Other causes have been ascribed as etiologic factors, such as, congenital, mycotic, arterial degeneration, atheroma, embolism, pregnancy, trauma, etc. In Sherlock and Learmonth's 74 cases, 46 per cent presented evidence of arteriosclerosis and 6 were apparently due to congenital causes. Cosgrove et al. reviewed 63 cases, found that 37 were explained by arteriosclerosis, 12 on a mycotic basis, 9 congenital, and 5 miscellaneous. It is believed that intra-abdominal pressure caused by advanced pregnancy predisposes to the formation of an aneurysm at the site of a congenital defect in the wall of the splenic artery. Though this causative factor is problematical, there is little doubt that the abnormal intra-abdominal pressure accounts for the frequency of rupture of the aneurysm during pregnancy.

In 9 of our 11 autopsied cases there were 4 males and 5 females. In 108 of the 114 collected cases, 25 were males and 83 were females. In 190 cases collected by Owens and Coffey, 127 were females and 63 were males. In all of the collected clinical cases recorded in the literature, females predominated with ratios of from 2:1 and 5:1. The greater preponderance of females in the surgical cases is accounted for by the frequency of rupture of the aneurysm occurring during pregnancy. In the autopsy studies the sex distribution was about equal. Sherwin and Gordimer likewise noted that in the older age group, the incidence of aneurysm of the splenic artery in the male and female sex was approximately equal.

In 9 of our 11 autopsied cases in which the age was given, the ages ranged from the 5th to the 8th decade. There were 3 in the fifth, 2 in the sixth, 3 in the seventh and 1 in the eighth decade. In 100 of the 114 collected cases, the ages ranged from 14 to 81 years. In our autopsy study the condition was found chiefly in middle and older age subjects. The collected cases showed a high incidence of splenic artery aneurysms in the younger age group. Over one third of the collected cases occurred below the age of 40. It is interesting to point out that of the 24 male cases, 19 occurred above the age of 50. On the other hand, fe-

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The author is indebted to Dr. Tobias Weinberg, Head of the Department of Laboratories of the Sinai Hospital for the privilege of using the autopsy material in this study.

males showed a preponderance in the younger age group. Of the 77 females, 51 cases occurred between the 2nd and 4th decades. Table 2 gives the ages in decades in the 100 collected cases.

TABLE II

SHOWS THE AGES IN DECADES IN 100 OF THE 114 CLINICAL CASES

Age Groups	Cases
10-20	2
20-30	20
30-40	20
40-50	14
50-60	15
60-70	23
70-80	5
80-90	1
Total cases	100

The site of the aneurysm in the splenic artery varies. In our 11 autopsied cases, 3 occurred in the main trunk, 3 in the hilum, 2 at the bifurcation, 1 in the branches, and in 2 the site was not specified. The vast majority of splenic artery aneurysms occur in the main trunk and hilum. Table 3 shows the site of the aneurysm in 61 of the 114 collected cases.

TABLE III

THE SITE OF THE ANEURYSM IN 61 OF THE 114 COLLECTED CLINICAL CASES

Site	Cases	Per cent
Main trunk	22	36.0
Hilum	21	34.4
Bifurcation	9	14.7
Branch	9	14.7

The size of the aneurysm sac varies from a minute microscopic sacculation to 15 cm. or more in diameter. In 5 of our 11 cases in which the size was given, it varied from 0.7 to 2.5 cm. in diameter. In 53 of the 114 collected cases the size ranged from 0.5 to 15 cm., with an average of 3.8 cm.

Splenic artery aneurysms are frequently multiple As many as 10 aneurysmal sacs have been recorded in one case. In 9 of our autopsied cases, there were 2 instances with multiple aneurysms, (two sacs each). In the 114 collected cases, 92 were single and 22 revealed multiple aneurysms. Of these, there were 7 with two sacs, 4 with three sacs, 2 with four sacs, 1 with five sacs, 1 with six sacs, 1 with 7 sacs, 1 with ten sacs, and in 5 the number of sacs was not specified.

In most instances the splenic artery aneurysm is not associated with aneurysms anywhere else in the arterial system. The association of an aneurysm elsewhere in the body with splenic artery aneurysm is rare. Nevin and Williams reported a case in which the splenic artery aneurysm was associated with multiple aneurysms of the Circle of Willis in the brain.

In our autopsy study, none of the 11 cases had shown evidence of a rupture of the aneurysm. However, in the clinical cases, there is an unusually high incidence of rupture of the aneurysm. In 114 collected cases, 56, or 49 percent were reported to have ruptured. The majority (75 per cent) of ruptures occurred within the greater peritoneal cavity, or involved the greater peritoneal cavity secondarily to an overflow of contents from the lesser peritoneal cavity. The site into which the rupture occurs depend upon the location of the aneurysm. Since the anatomic position of the splenic artery lies in a horizontal plane across the left upper abdomen, behind the stomach and lesser omentum, and along the upper border of the pancreas, it would appear that when the aneurysm ruptures, it should involve the lesser omental sac with greater frequency. Although a review of the collected cases shows a greater preponderance of greater peritoneal cavity involvement, in many of these cases this involvement was secondary to an overflow of blood from the lesser into the greater peritoneal cavity through the foramen of Winslow. Table 4 shows the site of rupture in 56 recorded cases.

TABLE IV

SITE OF THE RUPTURE INTO THE ADJACENT VISCERA IN 56 OF THE 114 CASES

	Cases
Greater peritoneal cavity	29
Lesser peritoneal sac	2
Greater and lesser peritoneal cavities	10
Greater per toneal cavity and retroperitoneal	1
Greater and lesser peritoneal cavities and retroperitoneal	2
Greater and lesser peritoneal cavities and pancreas	1
Splenic vein	3
Splenic vein, stomach and duodenum	1
Splenic artery	1
Stomach	4
Colon	1
Pancreas	1
Total cases	56

In the 114 collected cases, there were 83 females, and of these, 19, or 23 percent were pregnant. The majority of these occurred below the age of 40. See Table 5. The explanation for the rupture of the splenic artery aneurysm and the increased number occurring in women who were pregnant is no doubt due to the increased intra-abdominal pressure during the last phase of pregnancy. Lennie and Sheehan likewise noted that most of the cases occurred in the last trimester.

Splenomegaly is commonly associated with splenic artery aneurysm. This is probably due to the excessive hypertensive pressure within the splenic arterial sys-

TABLE V

AGES IN 19 CASES OF PREGNANCY ASSOCIATED WITH SPLENIC ARTERY ANEURYSM

Age Group	Cases
20-25	4
26-29	4
30-35	8
36-39	1
40	1
41	1
Total cases	19

tem. In 9 of our 11 autopsied cases, in which the size of the spleen was given, there were 3 instances with an enlarged spleen. In the 114 collected cases, there were 23 instances or an incidence of 20 per cent, with an enlarged spleen. Of 125 cases collected by Sherlock and Learmonth, 22, or 17.6 per cent presented evidence of an enlarged spleen.

Most splenic artery aneurysms are asymptomatic. Many of the aneurysms are discovered by routine x-ray examination of the abdomen. Large aneurysms may produce symptoms as a result of pressure on the adjacent viscera. In some cases there may be pain. Anemia is occasionally noted as a result of seepage of blood. In the larger aneurysms an expansile pulsating mass is often palpated. A bruit may be heard in the left upper quadrant. The spleen is enlarged in 20 per cent of cases. There may be vomiting and other digestive symptoms. Calcification of the aneurysmal sac often occurs as a result of calcific degeneration. It occurred in 4 instances in 9 of the 11 autopsied cases, in which the records were detailed and in which calcification was mentioned. In the 114 collected cases, calcification of the aneurysm was noted in 36 or 31.5 per cent of cases.

The roentgen examination often reveals evidence of splenic artery aneurysm because of the frequency of calcification of the sac. The calcification of the aneurysmal sac presents a densely defined periphery with a mottled center, giving it the appearance of a cracked egg-shell. The calcified or enlarged aneurysmal mass generally moves with respiration. When the aneurysm is large, it may produce pressure on the adjacent organs, which is recognized as an extrinsic pressure defect. In a case reported by Heriberto et al, the calcified aneurysm protruded out from the contour of the great curvature of the stomach, but it was shown to be situated behind the stomach. Aortography or angiography of the splenic artery may be employed as a diagnostic measure in establishing the diagnosis of splenic artery aneurysms.

In the differential diagnosis, other simulating conditions must be considered, namely, aneurysm of the left kidney artery, abdominal aorta aneurysm, echinococcus cyst of the left lobe of liver, spleen or mesentery, retroperitoneal mass, tumor or calcification of the left adrenal or left kidney.

CONCLUSIONS

1. In a study of 1,319 consecutive adult autopsies, 11 cases or an incidence of 0.8 per cent of splenic artery aneurysms was found.

2. In a collected series of 114 cases, females predominated. The incidence of 73 per cent females is not the true sex incidence, since a high incidence of pregnancy among the clinical cases was complicated by rupture, which necessitated surgical intervention, whereas among routine consecutive autopsy cases and the older age group, the sex is approximately equal.

3. Of the 114 collected cases, there were 83 females, and of these 19 or 23 per cent were pregnant.

4. In the collected clinical cases, over one third occurred below the age of 40. Most of the autopsied cases occurred in the older age group.

5. Splenomegaly is commonly associated with splenic artery aneurysm. It occurred in 3 of our 9 autopsied cases, and in 23 or 20 per cent of the 114 collected cases.

6. Rupture of the aneurysm occurred in 49 per cent of the reported 114 collected cases, and in none of our autopsied cases.

7. Calcification is commonly demonstrated in splenic artery aneurysms. It occurred in 4 of our 9 autopsied cases, and in 36 or 31.5 per cent of the 114 collected cases.

8. The diagnosis can often be made by means of the x-ray examination and confirmed by aortography or angiography.

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NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED: V. LIPIDOGRAM BY PAPER ELECTROPHORESIS IN "NORMAL PATIENTS" 80-100 YEARS OF AGE. A PRELIMINARY REPORT

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WITHIN THE past three years, we have had unusual experience with geriatric patients having general medical conditions of that age group such as cerebral and "generalized" arteriosclerosis, diabetes mellitus, peripheral vascular disease, and neurological conditions. These individuals were confined to this chronic disease hospital mainly for economic and social reasons.

We have published a preliminary report showing the correlation of serum lipid partitions and lipoprotein molecules (Sf 0-400) in "normal" patients 80-100 years of age (1, 2). There have been no similar published studies to date. Seventy-five such patients with no known past histories of metabolic, hepatic, nor coronary artery disease were included in this study.

Research in blood lipids has elaborated methods, which have been found invaluable in the investigation of pathological conditions with associated disturbances of the lipid metabolism. The use of these methods has been limited by the fact that they are fairly time-consuming, complicated, and require large amounts of blood. Recent studies endeavor for simple micromethods for routine use such as paper electrophoresis.

The present report endeavors to ascertain, for the first time, any correlation between paper electrophoretic and ultracentrifugal methods of serum lipids in such an age group.

Electrophoresis is the migration of charged particles in a fluid between electrical poles. This method has recently been used to study and to separate protein molecules. Electrophoresis provides the most convenient and dependable means of analyzing the protein content of the body's fluids and tissues. It has played an important role in clinical protein research.

Serum lipids do not occur in free form, but in combination with protein, as lipoproteins. Tiselius and his associates found that the blood fraction known as globulin was in reality of three substances. He named them alpha globulin, beta globulin, and gamma globulin (3, 4).

An inconspicuous function of the plasma proteins is that of transport. Almost every molecule that has to be carried from one part of the body to another travels on a protein. Most of the lipids in blood, for example, are bound in the form of alpha and beta lipoproteins, and protein is involved in the transport of fat from gut to liver.

The recent increase in our knowledge of the lipoproteins has been made possible by the development of a number of new methods. These methods may be conveniently considered under three headings:

1. COHN's chemical fractionation.

2. GOFMAN's ultracentrifugation.

3. Zone electrophoresis on paper or starch followed by elution and lipid analysis or paper electrophoresis with subsequent colouring of the lipids on the paper strip.

These three methods are based on different principles: Cohn's (5) method utilizes the varying solubility of the proteins; Gofman's (6) the difference in specific weight and size of the molecules; and the electrophoretical methods (3) the varying rate of migration of the proteins in an electric field.

Zone Electrophoresis

Within recent years a third technique of electrophoresis has developed. In the two described to date—microscopic (7) and moving-boundary electrophoresis—the particles flow in a liquid medium (3). The newer method flows them through a solid medium. The separated particles do not manifest themselves as moving boundaries but bunch together into zones in the solid; hence the method is known as zone electrophoresis. The solid most frequently employed in zone electrophoresis is filter paper (8, 9, 10, 11, 12, 13).

In a sense zone electrophoresis is like the separation method known as paper chromatography except that the separation factor is electricity instead of solubility.

Zone electrophoresis on filter paper is based mainly on the principle of moving boundary electrophoresis described by Tiselius (3, 4, 7). This method utilizes the difference in rate of migration of the various components of the serum proteins in a buffer solution of suitable pH in an electric field. It was the need of a simpler and less expensive equipment that led to electrophoresis in a filter paper medium.

Method of Study and Material

Two groups of patients were studied—group A (old age group) consisted of "normal" geriatric patients from 80 to 94, with an average age of 90 years. Group B (younger age group) ranged in age from 17 to 46, with an average of 33 years. The old age group had no metabolic, hepatic, nor coronary artery disease, but one of generalized arteriosclerosis. The younger age group had no cardio-vascular nor coronary artery

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disease. They were post-operative or psychoneurotic individuals and were studied for comparative purposes. (Tables I-II).

Forty cc. of fasting venous blood were withdrawn from each patient. Twenty cc. were utilized for the measurement of Sf lipoprotein molecules. Ten cc. were examined for serum cholesterol (Free, esterified and total), using the Schoenheimer and Sperry methods (14), lipid phosphorus using the Youngburg method (15). Total lipids were determined gravimetrically, by the modified Bloor method (16). In addition, blood sugar, creatinine, non-protein nitrogen and blood counts were also obtained. The remainder of the blood was used for zone electrophoresis studies. The apparatus was that developed by M. Wurm (17).

METHOD OF PAPER ELECTROPHORESIS STUDY

1. Seven lambda undiluted blood serum is streaked across 1.5 inches wide strips of Whatman 3 MM filter paper. The papers are held taut between plastic blocks.

2. The ends were immersed in diethylbarbiturate buffer, pH 8.6, 0.05 ionic strength. Four paper strips in parallel were placed in a plastic apparatus of the horizontal type, equipped with a hood to prevent evaporation.

3. Current of 100 volt and 4-5 milliamp (direct current) was passed through the apparatus at room temperature for 18.5 hours.

4. Strips are then removed and dried in an oven at 120° C. Duplicate strips were employed for each serum specimen; one being stained with bromphenol blue for the protein pattern and the other with Oil-Red O for the lipid distribution pattern.

5. The stained strips are then evaluated in a Photovolt Model 525 Densitometer. The areas under the individual peaks are measured with a polar planimeter and the relative concentration of the individual components computed from these area measurements. The planimeter is used for measuring the areas, obtaining the percentage of each component. The densitometer gives the component. The diethylbarbiturate buffer has a higher resolving power than the phosphate buffer. The latter can not resolve alpha$_1$ from albumin. The Oil-Red-O dye was used for coloring lipids, since it was claimed to be superior to the available dyes for such purposes (18).

The *serum proteins* occurred as five bands corresponding in the order of increasing mobility to gamma, beta, alpha$_1$ and alpha$_2$ globulins and to albumin. In some instances, beta 1 and beta 2 components were measured. Some have included alpha$_1$ and alpha$_2$

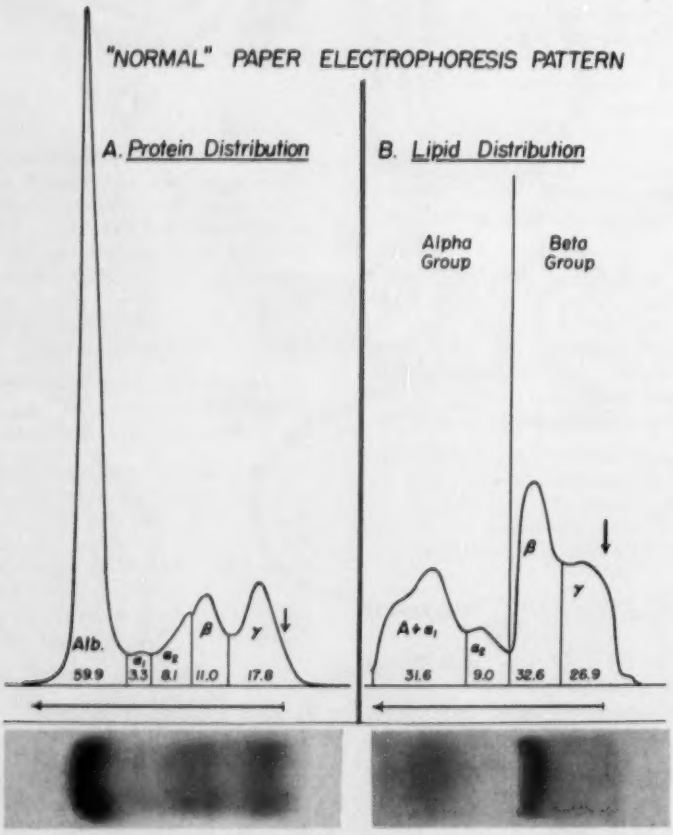

Fig. 1: Example of Normal Paper Electrophoresis Pattern Obtained in Patients 80-100 Years of Age. A—Protein Distribution. B—Lipid Distribution, designated into two groups, "Alpha" and "Beta."

into one component as alpha$_2$. We have designated beta 1 and beta 2 under the one heading of "beta" component. The most densely stained portion was noted in the albumin fractions, less in the beta and least in the other areas of alpha 1 and alpha 2 (Fig. 1A)

The lipid curve showed an intensely stained patch in the beta globulin region and a somewhat paler patch in the alpha$_1$ globulin region.

In the lipid curve four different components may be distinguished: (Fig. 1B) 1. The first peak occupies about 30 per cent of the area of the diagram. Its position suggests that it represents alpha 1 lipoprotein.

2. In the alpha 2 globulin band, the curve usually shows a small peak, covering about 10 per cent of the surface. It is represented by the alpha 2 lipoprotein peak.

3. The largest and most densely stained peak, occupying about 35 per cent of the diagram, is located in a position corresponding to the beta-globulins in the protein diagram. Its position in the diagram indicates that the peak represents beta - lipoprotein and contains 50-60% of the lipids.

4. The peak at the starting point is usually not distinctly separated from that of the beta-lipoprotein. It corresponds to the gamma region in the protein diagram. It is composed mainly of neutral fat and is probably made up of chylomicrons. Ten to 20% of lipids are in this region.

In the *lipid pattern*, (Fig. 1B), the lipids are concentrated in two regions of the protein spectrum. It corresponds to zone I (alpha group) = albumin, alpha 1 and alpha 2 globulin regions and Zone II = beta and gamma globulin regions. (Beta group). The alpha and beta globulins contain lipid, while the gamma globulin does not contain lipids. The albumin plus alpha 1 correspond to the alpha lipoprotein region. The beta and gamma globulins correspond to the beta lipoprotein region. Neutral fat is at the starting point of the gamma region. The alpha zone is shifted toward the albumin zone. The alpha lipid is located between the albumin and alpha 1 zones. There is little lipid in the albumin and alpha regions. The alpha lipoproteins do not show up distinctly in the protein pattern.

A normal paper electrophoretic pattern showing the protein and lipid distribution consists of albumin approximately 60%; alpha$_1$, 3%; alpha$_2$, 8%; beta 11%; gamma 18% (Fig. 1A). The lipid pattern demonstrates 60% lipids in the "beta" group (corresponds

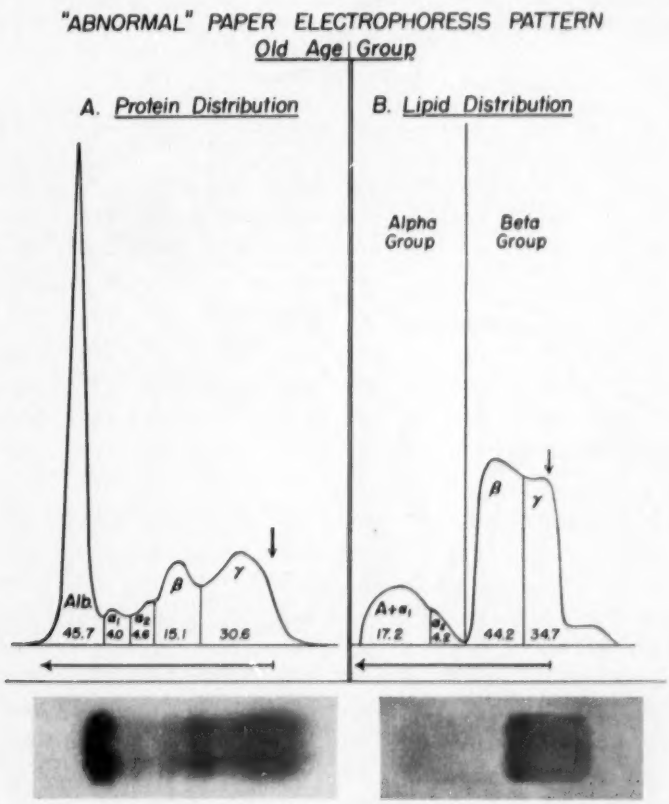

Fig. 2: Example of an Abnormal Paper Electrophoresis Pattern, in Patients 80-100 years of Age. A. Protein distribution, showing low Albumin and high Gamma Regions. B. Lipid distribution showing an increase in the "Beta" and decrease in the "Alpha" group values.

to region of beta and gamma proteins), and 40% in the "alpha" group (corresponds to albumin, alpha 1, and alpha 2). (Fig. 1B). An *"abnormal"* pattern shows in the protein distribution (of protein pattern) the gamma is high and the albumin low. (Fig 2A). In the lipid distribution there is an abnormal shift in the "beta" group. 80% of the lipids are in the "beta" group, while twenty percent are in the "alpha" group. (Fig. 2B).

A. *Old Age Group:*

Of the ten patients studied electrophoretically, 6 showed essentially a normal *protein distribution* pattern, whereas 4 showed an anomalous distribution. This was expressed in lowering the albumin level and a corresponding increase of the gamma-globulin level. (Patients number 7, 9 and 10) or an increase of the beta-globulin level (Patient No. 11).

The protein distribution in the serum of the old age group corroborated the findings of others. The A/G ratio and the relative albumin are smaller, while the beta globulin concentrations were greater compared to the younger age group (19). (Fig. 2A).

An abnormal lipidogram however was noted in only patients 10 and 11 in that the "beta" group was higher. This was not noted in patients 7 and 9 (Table I). (Fig. 2B).

B. *Youiger Age Group:*

The *protein distribution* pattern was within normal range. The *lipoprotein* pattern was abnormal in two patients Nos. 12 and 16 in that the "beta" group was increased. (Table I; Fig. 3B).

Lipid Distribution: The lipid as stained with Oil-Red-O was concentrated largely in two regions of the protein spectrum. The first corresponds to the albumin and alpha$_1$ globulin regions, while the other to that of the beta globulin and gamma regions. Inasmuch as lipoproteins are known to be absorbed on filter paper, the color present in the gamma region may actually represent a trailing of the beta lipoprotein band. The lipoprotein of higher electrophoretic mobility seems to be concentrated somewhere between the albumin and alpha globulin protein bands. This groups the lipoprotein material into "alpha" and "beta" globulin classes. (Table I; Fig. 1B). (Fig. 3B).

The relative lipoprotein distribution by paper electrophoresis into "alpha" and "beta" groups has been noted by others especially Rosenberg and his asso-

TABLE I

PROTEIN AND LIPOPROTEIN DISTRIBUTION IN THE BLOOD SERUM OF HUMAN SUBJECTS BELONGING TO TWO DIFFERENT AGE GROUPS AS DETERMINED BY PAPER ELECTROPHORESIS

A. Old Age Group

No.	Name	Sex	Age Yrs.	Relative Protein Distribution					Ratio	Relative Lipoprotein Distribution		
				Alb.	α_1	α_2	β	γ	A/G	Group α	Group β	Ratio β/α
2.	E. V.	F	80	54.0	4.3	7.88	14.9	19.1	1.17	30.2	70.4	2.3
3.	M. M.	F	92	51.1	4.3	10.0	6.1	28.6	1.05	45.8	50.3	1.1
4.	A. H.	F	93	56.7	4.7	12.7	12.1	13.9	1.31	32.2	67.9	2.1
5.	R. B.	F	91	59.9	3.3	8.1	11.0	17.8	1.49	40.6	59.5	1.4
6.	J. L.	M	90	54.0	6.8	8.0	14.2	17.0	1.17	28.6	71.4	2.5
7.	W. B.	M	82	43.3	4.1	10.9	10.9	30.9*	0.76	40.7	58.8	1.4
8.	M. G.	M	94	52.6	3.9	9.1	12.3	22.3	1.11	34.9	65.6	1.9
9.	H. C.	M	94	43.0	3.8	10.2	11.6	31.4*	0.75	40.1	60.2	1.5
10.	F. M.	M	93	45.7	4.0	4.6	15.1	30.6*	0.84	21.4	78.9*	3.7
11.	B. M.	M	89	42.0	6.9	10.7	18.3*	22.1	0.74	13.6	86.5*	6.3
	Average		90	50.2	4.6	9.2	12.6	23.4	1.04	32.8	66.9	2.4
				B. Younger Age Group								
12.	S. C.	M	44	61.0	3.3	9.7	13.5	12.5	1.56	18.8	81.3*	4.3
13.	J. G.	M	46	a) 54.1	4.8	11.2	13.6	16.3	1.18	33.7	67.3	2.0
				b) 57.8	3.5	6.8	13.3	18.5	1.37	37.1	63.2	1.7
14.	M. M.	M	33	67.8	5.0	6.0	8.5	12.7	2.10	39.8	60.2	1.5
15.	I. P.	F	17	56.1	4.2	6.6	12.2	20.8	1.28	30.1	69.8	2.3
16.	P. R.	F	25	63.9	4.2	5.9	10.5	15.5	1.77	21.1	79.9*	3.7
17.	M. W.	F	35	61.7	3.5	8.5	9.4	16.9	1.61	25.6	75.2	2.9
	Average		33	61.0	4.0	7.6	11.2	15.9	1.59	28.5	71.9	2.7

*Increased Values

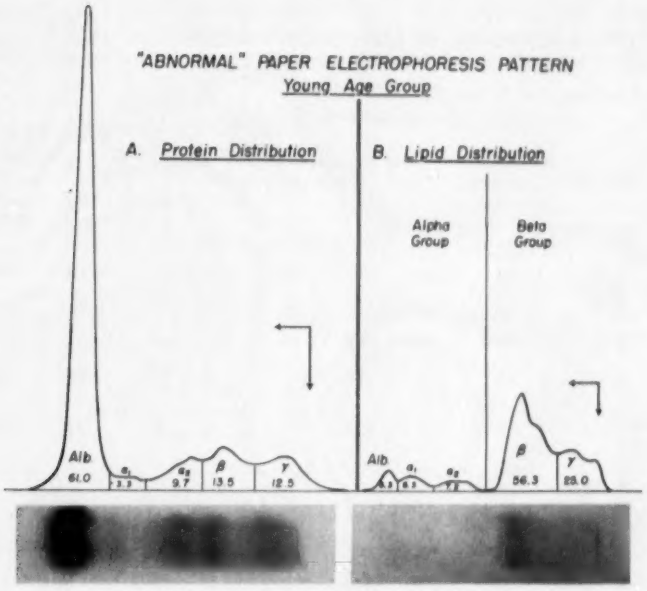

Fig. 3: Example of an abnormal Paper Electrophoresis Pattern in Normal Patients, 17-46 Years of Age. A. Protein distribution—Normal. B. Lipid distribution shows increased "Beta" and decreased "Alpha" group values.

ciates. The abnormal lipidogram revealing an increase in the "beta" group in the four patients mentioned above was observed by Rosenberg et al (20). in patients having coronary and arteriosclerosis and not in normal control patients. However, two such abnormal lipidograms were found in our younger age group (patients 12 and 16) and only in two of our old age group (patients 10 and 11). If this is characteristic for arteriosclerosis, then an abnormal lipidogram with an increase in the "beta" group should have been obtained in most of our old age group. Undoubtedly, all of the patients in the old age group have arteriosclerosis.

The average values for the "alpha" and "beta" groups as well as the ratio of the beta to alpha lipoproteins were practically the same in both the old age and younger age groups. (Table I).

THE LIPID AND SF-LIPOPROTEIN DISTRIBUTION

As mentioned above, our knowledge of the lipoproteins has been increased by a number of methods. The ultracentrifuge technique as elaborated by Gofman and his group (6), is based on the difference in specific weight and size of the molecules. The fractions were named according to their migration in Svedberg's units ($1\ s = 10^{-13}$ cgs. units) and were measured in flotation units. (Sf). The atherogenic index as postulated by Gofman is a single number descriptive of an individual's atherogenic potentialities (21).

The arithmetic mean values of the serum lipid partitions, Sf lipoprotein molecules, and the atherogenic index in normal patients (young and old) may be noted in Table II. Increase in all of the Sf molecules is noted in only three patients (S. H., No. 4); (R. B., No. 5); and (F. M., No. 10) in the old age group. The atherogenic index was also increased in these patients.

The lipid partitions and total lipids were lower than those in the middle aged individuals as reported by us (Table II) (2a). This further confirms the observations that an increase of the Sf. lipoprotein molecules need not be accompanied by an increase in the total cholesterol nor lipid partitions, and vice versa (22, 23).

There was no increase in values of such Sf molecules in the younger age group (Table II).

The *lipidogram* was found to be abnormal in patients F. M. (No. 10); B. M. (No. 11); S. C. (No. 12) and P. R. (No. 16). There was an increase of the "beta" group above the average of 66.9% in the old age group and 71.9% in the young age group respectively. A corresponding increase of the Sf lipoprotein molecules and abnormal lipoprotein distribution by paper electrophoresis was found in only one patient in the old age group (F. M., No. 10). It is of interest to note that the lipidogram was abnormal in two patients from the normal younger age group. (S. C., No. 12) and (P. R., No. 16). (Table I and Fig. 3B).

DISCUSSION

In the majority of aged individuals, the protein pattern shows the "beta" globulin level to be higher than that reported for healthy young adults. The beta-globulin fraction contains an appreciable percentage of serum lipids bound in the form of beta lipoproteins (24). It was suggested that the increase in the concentration of this protein component is related to the higher cholesterol levels found in aged atherosclerotics (25). One purpose of this present investi-

TABLE II

SERUM LIPID PARTITIONS, SF LIPOPROTEIN MOLECULES, AND ATHEROGENIC INDEX IN TWO DIFFERENT AGE GROUPS. (MALE AND FEMALE)

A. Old Age Group

(Increased Values*)

No.	Name	Age Years	Sf Lipoprotein Molecules Mg per cent 0-12	12-400	12-20	20-100	Atherogenic Index (Units)	Serum Lipid Partition Mg per cent Total Lipids	Total Cholesterol	Phospholipids
	Female									
2	E. V.	80	208	37	15	8	28	487	173	150
3	M. H.	92	335	40	28	6	40	634	266	187
4	A. H.	93	424	213	64	114	80*	575	238	127
5	R. B.	91	431	189	55	102	76*	649	252	152
Mean Average (Ref. 1, 2)	Female Patients	80-100 Years	305	128	43	46	53.2	645	230	192
	Male									
6	J. L.	90	240	174	39	66	55	521	177	192
7	W. B.	82	284	126	40	28	50	576	198	194
8	M. G.	94	287	150	37	20	55	619	184	201
9	H. C.	94	281	35	28	8	24	596	260	175
10	F. M.	93	444	277	64	73	93*	595	178	190
11	B. M.	89						861	197	218
Mean Average (Ref. 1, 2)	Male Patients	80-100 Years	293	131	36	43	53	611	203	194

B. Young Age Group

	Male									
12	S. C.	44	366	215	50	132	74			
13	J. G.	46	280	97	22	60	45			
14	M. M.	33	395	142	46	70	64			
Mean Average (Ref 30, 31)			361	206	75	108	74			
	Female									
15	I. P.	17	297	90	44	37	45			
16	P. R.	25	367	40	31	3	44			
17	M. W.	35	473	42	4	33	55			
Mean Average (Ref. 30, 31)			304	187	53	63	51			
For Normal Middle Aged Patients (Ref. 2A)								861	197	218

gation was to determine whether the rise in beta-globulin in aged patients' sera is related to the increased level of specific macro-molecular lipoprotein components (*26*). For these reasons, some correlation between paper electrophoretic and ultracentrifugal studies was sought.

The extreme simplicity of the apparatus required for the electrophoretic separation of serum proteins on filter paper makes it possible for such a specialized diagnostic tool to be used more frequently than the complicated methods of the moving boundary type electrophoresis. As a rule, the gamma globulin values determined by paper electrophoresis are somewhat higher than those obtained by the Tiselius moving boundary method, possibly due to some adsorption of protein near or at the starting line. In contrast to the classical moving boundary technique the paper strip method makes it possible to obtain some information on the distribution of proteins as well as lipid material in the serum of the subjects under study (*27*).

The paper strip results were compared with chemical lipid determinations and the lipoprotein Sf values

obtained with the ultracentrifuge. There is no clear-cut correlation between these data and the lipid distribution diagrams as obtained by paper electrophoresis. If one assumes that Oncley's (28) beta lipoprotein is contained in the Sf O-12 class of molecules and if the "beta" and "gamma" designated areas on the paper lipidograms are due largely to Oncley's lipoproteins, one would expect to find that a relatively large concentration of Sf O-12 lipoprotein molecules would be reflected in a relatively large proportion of "beta" and "gamma" lipid material on the paper electrophoretic pattern. This was not found. Similarly high Sf 12-400 values do not seem to be correlated to significantly high relative concentrations of any of the lipidogram components. Theoretically, this is not surprising, since the ultracentrifuge is mainly sensitive to the density and the molecular weight of large molecules, whereas electrophoretic mobility depends on electrochemical properties (surface charge density).

As to absolute lipid determinations, paper electrophoresis is not basically suitable for other than relative distribution studies. This is not superior to chemical determinations for specific substances.

The values obtained for the individual lipoprotein components have been grouped together under the heading "alpha" and "beta" groups respectively. A more detailed analysis is not justified at this stage, since the so-called gamma lipoprotein band in the lipid distribution diagram is probably a composite of some trailing of the beta lipoprotein material due to adsorption and of some neutral fat (chylomicron) particles. Gamma globulin itself is known not to contain significant amounts of lipids. The same is true for pure plasma albumin although, in some earlier work, Tiselius and his associates did report the presence of some cholesterol in plasma albumin (4). The cholesterol and phospholipid distributions in the lipoprotein components by paper electrophoresis have been recently studied (29).

The averages listed indicate that there is little, if any, significant difference between the lipoprotein distribution in the lipidogram in the two age groups examined.

The statistical significance of the differences in protein distribution in the two age groups studied here is similar to that carried out by the classical moving boundary method of Tiselius. Thus, the appreciable difference in the A/G ratios found here for the two age groups is definitely significant (19).

SUMMARY AND CONCLUSIONS

1. Serum lipid partitions, standard Sf lipoprotein molecules, and atherogenic index were found to be low in normal patients, age 80-100 years.

2. The paper electrophoresis is a simpler method than the ultracentrifuge for studying the distribution of protein and lipid material in the serum.

3. The present report ascertains, for the first time, any correlation between paper electrophoretic and ultracentrifugal methods of serum lipids in such an age group.

4. Two groups of normal patients were studied, with an average age respectively of 33 and 90 years.

5. The protein distribution shows a lower albumin and A/G ratio; and a higher beta globulin value in the old age group.

6. There is no significant difference between the lipoprotein distribution in the two age groups examined.

7. Abnormal lipidograms, showing increase in the "beta" lipoprotein group, were found in only two patients from the old age group and two patients from the younger age group, respectively.

8. The increased "beta"-lipoprotein values did not occur in these old age group patients having an increased Sf lipoprotein molecules and increased serum lipid partitions.

9. There is no clear-cut correlation between the chemical serum lipid partitions; Sf-lipoprotein molecules by the ultracentrifugal method; and the lipid distribution diagrams (lipidogram) by paper electrophoresis.

10. Lipidograms by paper electrophoresis in normal patients, age 80-100 years, are herein reported for the first time.

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ABSTRACTS ON NUTRITION

JACOBI, H. G.: *The food consumption of juvenile diabetics. Evaluation of diets used at home and at summer camp.* Am. J. Clin. Nutr., 2, 5, Sept.-Oct., 1954, 343-347.

Dietary histories on 62 girls and 58 boys indicated that, while at home, more of them were consuming far more carbohydrate than was specified in their prescribed diets, and also that frequently the prescribed diets were deficient in total calories. About half of the 37 children on "free diets" were found to be consuming what was regarded as normal and adequate, while the other half were in excess.

MAYER, G. A., CONNELL, W. F., DEWOLFE, M. S. AND BEVERIDGE, J. M. R.: *Diets and plasma cholesterol levels.* Am. J. Clin. Nutr., 2, 5, Sept.-Oct. 1954, 316-322.

Feeding experiments on healthy male subjects indicated that dietary cholesterol had no effect on plasma cholesterol levels, whereas alterations in the level of dietary fat, whether of animal or vegetable origin, led to parallel changes in plasma cholesterol.

GRUSIN, H. AND KINCAID-SMITH, P. S.: *Scurvy in adult Africans.* Am. J. Clin. Nutr., 2, 5, Sept.-Oct. 1954, 323-335.

Thirty cases of scurvy in adult Africans were studied in the space of one year. The disease commonly presented as an affection of the legs together with evidence of general bleeding and/or hypertrophic gums. Six cases presented with isolated hemorrhage into muscle or gums. Scurvy in Africans may be responsible for some cases of isolated hemorrhage from bowel, kidney or serous cavities. In 2 patients, extensive chronic changes were found in a leg which had been the seat of acute scurvy 2 to 3 years previously. Some patients showed osteoporosis of bones. Blood proteins and liver function tests were abnormal in all patients. Some patients showed generalized edema; others showed elevated jugular vein pressure and fluctuations of hemoglobin levels during the acute attack. It is suggested that these may be signs of variations in blood volumes.

JOSEY, W. E.: *The role of nutrition in the management of pregnancy: a review of recent studies.*

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Am. J. Clin. Nutrition, 2, 5, Sept.-Oct. 1954, 303-315.

Great differences of opinion exist among authorities as to how much nutrition influences pregnancy, Burke maintaining that prenatal nutrition is intimately related to the course and outcome of pregnancy, while the Vanderbilt group could find no clear-cut indication that maternal dietary deficiencies could be linked to the wide variety of obstetric and fetal abnormalities studied. It appears that obesity tends toward toxemia of pregnancy while underweight tends toward premature labor. Anemia tends to prolong labor. Protein deficient diets may tend toward the development of toxemia. High protein intake results in healthier infants. Vitamin C and hesperidin appear useful in habitual aborters. The mother should use plenty of calcium during pregnancy. Further study is needed on the effects of potassium on toxemia.

BOSE, A. N. AND BOSE, S.: *An environmental factor influencing the toxicity of intravenous iron.* J. Indian Med. Assn., 23, 12, Sept. 1954, 547.

Working with white mice and using test doses of 100 mg. per kilo, Indian and foreign preparations of iron for I. V. use were employed. It was observed that the lethal dose of any particular sample varied with the season. A dose which was low in toxicity during winter gave high mortality figures in the hot summer months. Consequently, if intravenous iron is used in the tropics, this important relationship between toxicity and environmental temperature should be borne in mind.

SUBRAMANIAN, R. AND MENON, M. S.: *Hyperinsulinism—a case of islet cell tumor of the pancreas.* J. Indian Med. Assn., 23, 12, Sept. 1954, 537.

The authors present an interesting case of a man aged 35 who was subject to spells of unconsciousness. A random blood sugar check showed 37 mg. per cent. A glucose tolerance test showed an extremely flat curve, with an initial reading of 30 mg. and the peak reached in ½ hour at 60 mg. Operation revealed a non-malignant insuloma of the body of the pancreas which was easily removed by blunt dissection. Histologically the tumor consisted entirely of islet cells without ducts. The cells were of the beta type. He made a perfect recovery and has had no further attack in the year that has elapsed since operation. The authors feel that all that diagnosis requires is marked hypoglycemia induced by fasting and relieved by food.

GUPTA, C. R. AND BASU, P.: *Liver function tests in nutritional anemias.* J. Indian Med. Assn., 23, 12, Sept. 1954, 542.

Composite liver function tests were done on 20 cases of pernicious anemia and 6 cases of nutritional megaloblastic anemia. Detoxifying function of the liver as measured by the hippuric acid excretion test was found diminished in all types of anemia. Anoxia was probably responsible for this result in many of the cases, as the test was normalized by a return of the blood counts to normal. The authors feel, however, that anoxia is not the whole story as other factors may influence the liver function, although such factors are not understood. (The authors do suggest that in some instances faulty liver function may have been a causal factor in the anemias—Reviewer).

FAWNS, H. T. AND ALDRIDGE, A. G. V.: *Methemoglobinemia due to nitrates and nitrites in drinking water.* Brit. Med. J., Sept. 4, 1954, 575-576.

Those members of a family who used solely the water from the well all showed levels of methemoglobin far above the upper limit of the normal range. A baby who had been receiving town water for 4 months, and the father, who ate at canteens during the day, both gave negative results. Where the water supply of a family is high in nitrates and nitrites, a young baby is more prone to show the effects of methemoglobinemia than its elders, as its daily water intake is proportionately much greater. Symptoms may be precipitated by the onset of a pyrexial illness, increasing oxygen demands. If a baby from a rural area shows cyanosis unexplained by the physical examination, investigation of the water supply may prove to be time well spent.

FRIEDMAN, M. AND BYERS, S. O.: *Observations concerning the production and excretion of cholesterol in mammals. XIV. The relationship of the hepatic reticuloendothelial cell (Kupffer cell) to endogenously produced cholesterol.* Circulation, 10, 4, Oct. 1954, 491.

The possible role of the hepatic reticuloendothelial system in the synthesis as well as the disposition of endogenously produced cholesterol was studied in the rat by various means. The results suggest that this system does not synthesize significant quantities of cholesterol nor participate in the egress of endogenously produced cholesterol from the plasma into the liver. It does, however, play an important, perhaps indispensable role in ridding blood of cholesterol derived from the diet.

EDITORIAL

CHRONIC CHOLECYSTITIS WITHOUT STONES

Since about 70 percent of gallbladders which do not concentrate cholecystographic media contain stones, either apparent or non-opaque, it would appear that a person suffering from symptoms characteristic of cholecystitis stands at least a 70 percent chance of benefit from cholecystectomy, provided the gallbladder is not visualized after several attempts. Actual experience tends to corroborate this theory, and today there is a growing tendency to remove non-visualized gallbladders which appear to be symptom-producing.

In cases of symptom-producing gallbladders which can be more or less well-visualized and in which no

calculi are seen, the present trend has been to treat them "medically," although, in a sense, we have no very good method for the medical treatment of chronic cholecystitis. It is true that spontaneous recovery sometimes occurs, in which case credit is given to whatever mode of treatment was used. The modified Meltzer-Lyon drainage (magnesium sulfate) and the use of nitroglycerine following the ingestion of cream, do seem, at times, to be of benefit, particularly when used intensively. A low fat diet, while obviously illogical, brings comfort to the dyspepsia of these patients, although a second school of thought recommends periodic high fat intake to induce drainage. The use of bile salt preparations daily likewise tends to improve symptoms. By none of these methods, however, is there any certainty of obtaining a cure of chronic cholecystitis.

Better yet, the concept of "biliary disease" involving the liver and ducts as well as the gallbladder in the disease, may be recommended for a trial through the use of lipotropic agents, high vitamin intake and high protein diet. Such a regime may ablate symptoms after a few weeks' trial.

However, one cannot see the reason for refusing surgery to the patient who is suffering from cholecystitis even though his gallbladder can be visualized and seen to contain no calculi. Perhaps the chronicity of the disease, its associated dyspepsia and general catabolic influences (weight loss), are as important indications for surgery as the presence of stone. In a high proportion of such cases, the gallbladder will be found abnormal on pathological study, and we know that a high proportion of these patients profit from the operation of cholecystectomy.

BOOK REVIEWS

SANDOZ ATLAS OF HEMATOLOGY. SANDOZ BLOOD ATLAS. 68 Charlton St., New York 14, N. Y. $7.00.

The Sandoz Company is distributing this blood atlas at cost to those who want it. The numerous and remarkable color reproductions of blood smears are worth the price. Practically all phases of blood morphology are dealt with. All color plates are made from actual blood smears as found in clinical cases. A careful study of these pictures will assist any practitioner in recognizing the various abnormal and normal white and red blood cells encountered in his practice.

SURGERY OF THE PANCREAS. (DIE CHIRURGIE DER BAUCHSPEICHELDRUESE). Prof. Dr. Gerhart Jorns. 144 pg., 34 illustrations, Walter de Gruyter & Co., Berlin, 1954. DM 19.80.

Jorns discusses the surgery of the pancreas in his book, published in German. The first part deals with the anatomy and physiology of the pancreas. The second part deals with the pathology and surgery of this organ. The clinical findings are thoroughly discussed. The roentgenological examination has not received the attention that it is given in the American literature.

The print and the illustrations are good. The material is well organized and covers the subject very well. We can recommend this book to all those interested in this field.

Franz J. Lust.

INCORRECT CLINICAL DIAGNOSES. (KLINISCHE FELDIAGNOSEN). M. Buerger, Leipzig. 550 pgs., 214 illustrations, partly in color. Georg Thieme Verlag, Stuttgart 1954. $14.75.

This is the second edition of an excellent book which was first published only two years ago, which shows how appreciated it has been far and wide. It is an extremely practical book. The presentation of the cases is clear. The new edition has been enlarged and deals with 49 new cases. Some new chapters have been added, such as the wrong interpretation of negative roentgenological findings. The 214 illustrations, six of which are in color, are very well reproduced and of the highest quality.

We can congratulate Buerger on this publication, which can be recommended to internists, surgeons and practitioners. The print and paper are of the best quality, by which the Thieme Publishing House is known to publish its books.

Franz J. Lust.

THE STOMACH. (L'ESTOMACH). Guy Albot and F. Poilleux. Masson et Co. Paris. 1954. 328 pages, nearly 200 illustrations.

This is the latest volume of the Actualites hepato-gastro-enterologiques de l'Hotel-Dieu in Paris and contains papers and presentations from this very well known hospital. There are many collaborators such as C. Auguste, G. Berthet, M. Cachin, J. Charrier M. Chiray, A. Cornet, Ch. Debray, E. Delannoy, R. Dupuy, G. Edelmann, Cl. Frileux, J. Gosset, R. A. Gutmann, P. Hillemand, A. Lambling, R. le Canuet, J. L. Lortat-Jacob, J. Mialaret, and J. C. Rudler.

Many topics are discussed, such as: Conditions after gastrectomy for ulcer, tumors of the region of the esophago-cardia junction, gastro-jejuno-colic fistulae, hypertrophic muscular stenosis of the pylorus, endoscopic and histologic diagnosis of gastritis, haemorrhages from the upper part of the stomach, comparison between radiology and gastroscopy in gastric pathology, gastroenterostomy in the treatment of ulcer, hernia diaphragmatica, and true and false ulcers of the gastrectomized patients.

The material is very well presented. The radiographs are excellent, and can be compared with many reproductions of specimens. The book is in French and can be highly recommended to internists, gastroenterologists and surgeons. The print is very clear.

Franz J. Lust.

AMER. JOUR. DIG. DIS.

GENERAL ABSTRACTS OF CURRENT LITERATURE

FITZHERBERT, J. C.: *Volvulus of the cecum.* Med. J. Australia, Aug. 7, 1954, 213-216.

Fitzherbert presents 17 cases of volvulus of the cecum. He indicates that the condition is a cause of abdominal pain more frequently than has been realized. Volvulus may be acute and irreversible, acute and reversible, or partial and intermittent. The pain when present is almost always associated with some distention of the lower abdomen. The pain disappears quite suddenly and as it disappears there is a rumbling of wind and a large amount of flatus is passed. A rectal examination can be diagnostic.

MCHARDY, G.: *Non-calculous biliary disease.* Amer. Prac. & Dig. Treat., 5. 9, Sept. 1954, 699-701.

Non-calculous biliary disease exists in about 20 percent of cases of extrahepatic biliary disease, and of these cases about one-third can be well-treated medically. (Acute cholecystitis is a surgical emergency). Surgery should be reserved for medical failures. Postcholecystectomy syndromes are more easily managed than chronic cholecystitis.

ALBOT, G., DUPUY, R., HERMAN, J. AND CORTEVILLE, M.: *From steatosic hepatitis to cirrhosis; a critical study of the role of steatosis in the development of cirrhosis; modalities in evolution proper to alcoholic steatosic cirrhogenous hepatitis.* Semaine Hopitaux Paris, No. 40, June 22, 1954.

1. Hepatitic steatosis may vary in development, sometimes regressing with no anatomic or biologic sequela, sometimes, conversely, ending in cirrhosis.

In the stage of isolated anatomic steatosis only can the functional investigations afford an element of appraisement about the prognosis, as the steatosis cytologically conceals the parenchymatous hepatitis when this is present.

2. In the authors' observations the following points are to be emphasized:

When the steatosis ends in cirrhosis, there is in this development an intermediate stage of diffuse parenchymatous and mesenchymatous hepatitis biologically and anatomically well characterized. In such cases an opposition in evolution is to be noted between the steatosis on the one hand, the hepatitis and sclerosis on the other hand. Thus does the steatosis protect the parenchyma from cytolysis and sclerosis.

In this protective role of the fat it is possible that the support mechanism of the trabecula as constituted by the steatosis infiltration might assume an important part.

In the authors' observations no element appeared in favor of the eventual role of the steatosis in the occurrence of the cellular degeneration.

3. Steatosis is by itself neither an evidence of cell degeneration nor an element required for the development of cirrhosis (as proved by the 4 cases reported in the preceding paper). The only immediate and required factor for the development of cirrhosis is the cytolytic hepatitis, whether or not overloaded with steatosis.

THERE IS BUT ONE CIRRHOTIC PROCESS

4. Yet steatosic cirrhogenous hepatitis differs from the cytolytic cirrhogenous hepatitis because of its course made up of successive evolutionary waves, the susceptibility of the steatosis to lipotropic drugs, the possibility of prolonged stabilizations going as far as to the aspect of residual cirrhosis biologically compensated.

MARSHAK, R. H., WOLF, B. S. AND ADLERSBERG, D.: *Roentgen studies of the small intestine in sprue.* Am. J. Roentgen. 72, 380, Sept. 1954.

Forty patients with sprue have been studied clinically and roentgenologically over a period from one to 17 years. The chief symptoms and signs included steatorrhea, weight loss, anemia, oral lesions, hypocalcemia, hypoproteinemia, flat vitamin A and glucose tolerance curves and normal pancreatic enzyme studies. Three patients revealed a normal small intestinal pattern. The remainder exhibited two distinctive patterns. The first and most characteristic was observed in 70% of the patients in this series and consists of dilatation most prominent in the middle and distal jejunum, segmentation, large 4-10 cm long barium filled loops of ileum best visualized during the evacuation of the barium meal, thickening of the mucosal folds and the presence of hypersecretion of an altered quality. While each of these features may occur in a wide variety of disorders, they are more frequent in and more pronounced in sprue. In the second pattern, segmentation is marked, early and persistent and present throughout the small intestine, secretions are pronounced and dilatation is slight to moderate. This latter pattern occurred in only 10% and is also observed on occasion in those conditions and diseases simulating sprue: namely, nephrosis, hyperthyroidism, cirrhosis, pancreatic steatorrhea, pellagra and other deficiency states. Roentgen evidence of improvement in the sprue pattern was significant in three patients following steroid therapy to the present time and in four patients who have been treated for many years with antianemic therapy. The "sprue pattern" is sufficiently distinctive roentgenologically to separate it from the heterogeneous group of conditions heretofore labeled with the roentgen diagnosis "irritation pattern," "enteropathy in deficiency states," "deficiency pattern," or disordered motor function.

Franz J. Lust, M.D.

LEMAIRE, A., HOUSSET, E., CASASSUS P. AND SEE, PH.: *Oxymetric study of the portal blood.* Presse Médicale 62, No. 45-19, June 1954, p. 945-946.

Barcroft, Schwiegk and Blalock have measured portal oxymetry in animals in order to judge the re-

spective parts played by the portal vein and the hepatic artery in bringing blood to the liver. Schwiegk mentioned in his research in 1932 that the percentage of saturation in oxygen of the portal blood is on an average 60%.

Leaving aside the work of Bierman and Coll, 1953, who by transcutaneous puncture took samples of portal blood from patients free from all hepatic disorders and found the same figure of 60%, we do not know of any sample of oxygen taken directly from the portal blood supply of a normal or pathological human being.

The authors set themselves the task of studying the portal blood in order to compare its saturation in oxygen, hematocytes, hemoglobin and globular figure. With patients free from hepatic disorders blood was taken from the portal vein during abdominal operations (e.g. gastric ulcer). In 6 cases there was 60% oxygenation.

In the case of three patients suffering from Cruveilhier-Baumgarten's cirrhosis the authors took blood which can be considered as portal blood from the level of the varicose veins of the abdominal wall and found a percentage of saturation between 65 and 87%, that is on an average 76% in 8 tests. In one of these cases the percentage increased during the development of the cirrhosis and passed from 65 to 87%.

With 5 patients suffering from alcoholic cirrhosis without any special malformation of the umbilical venous system but showing well-developed collateral abdominal circulation, blood taken from the collateral veins showed percentages from 63 to 72.

The writers emphasize that in the case of every patient the peripheral blood taken at the same time as the portal blood gave figures from 35 to 40% and that at the removal of each sample the hemoglobin, globular volume and the globular figure were the same in the two samples of blood.

They conclude:

1 that the portal blood in a normal person contains more oxygen than the peripheric blood;

2 that the portal blood of cirrhotics has a higher percentage of oxygen than that of a normal person and that the percentage of oxygenation of the portal blood increases during the development of the cirrhosis;

3 they think that this strange phenomenon can be explained by arterio-venous shunts notably in the spleen.

These conclusions are contrary to the notion of portal stasis so currently invoked in cases of cirrhosis of the liver. The manometric measurements which they have carried out confirm on the contrary the existence of portal hypertension.

STEEDE, F. D. F. AND SMITH, W.: *Staphylococcal food-poisoning due to infected cow's milk.* Brit. Med. J., Sept. 4, 1954, 576-578.

Two outbreaks of staphylococcal food-poisoning caused by clotted cream prepared on two different occasions from the milk of the same cow are described. Staph. pyogenes was found to be present in the milk from one of the quarters of the cow's udder on several occasions. The same type of staphylococcus also was isolated from the nose of the milker. The character of these strains of staphylococci more closely resembled strains of human than bovine origin.

FISHER, E. R. AND WHITMAN, J.: *Whipple's disease: report of case apparently cured and discussion of the histochemical features.* Cleveland Clinic Quart., 21, 4, Oct. 1954, 213.

Intestinal lipodystrophy, first described by Whipple, is a rare disorder. The clinical manifestations are less well defined than the pathological features. The onset of the disease is insidious, marked by periodic polyarthritis or arthralgia and, at times, chills and fever. Diarrhea usually occurs at some time during the disease but it is often not a prominent feature. Pigmentation of exposed skin areas, low blood pressure, loss of weight and peripheral lymphadenopathy are among the physical findings. Histologically the lesions are characteristic, and consist of a marked infiltration of the lamina propria of the small bowel by histiocytes that often line cystic spaces of varying size. The cytoplasm of these histiocytes stain strongly with the periodic acid-Schiff stain. A case is reported in which those features were present. Definite fragmentation and segmentation of the barium pattern of the small bowel were present. Much of the paper is devoted to the histological features of the histiocytes. The characteristic substance in these cells appears to be a mucopolysaccharide. It is especially interesting to note that a combination of deep x-ray treatment and nitrogen mustard has produced a four-year cure in this patient.

CHANCE, D. P., HOOD, R. T. AND WAUGH, J. M.: *Acute intestinal obstruction secondary to Meckel's diverticulum: Report of 9 cases.** Proc. Staff. Meet. Mayo Clin., Oct 13, 1954, 567.

In 5 months of 1952, 3 patients with acute intestinal obstruction were seen on the emergency surgical service at the Clinic. At operation, a complication of Meckel's diverticulum was found to be the cause of the obstruction. In the records of the Clinic from 1940 to 1952, inclusive, we found the details of 6 other similar cases.

The manner in which the intestine became obstructed in these 9 cases divides them into 3 groups: group 1 consisted of 3 cases. The obstruction was secondary to peptic ulceration, with perforation in 2 cases and diverticulitis with perforation in 1 case. The localized inflammatory process, by edema, compression, angulation and production of regional ileus, resulted in complete obstruction of the ileum. Group 2 consisted of 4 cases. The diverticulum or its terminal ligament was attached to a viscus, thereby producing an internal foramen through which prolapsed a loop of small bowel which became obstructed. Group 3 consisted of 2 cases. The diverticulum was the leading point of an intussusception.

In 8 of these cases the diverticulum was excised. In 2 of them the ileum was closed transversely. In 6 of them a portion of ileum, or of ileum and colon, was

*Abstract of paper published in A.M.A. Arch. Surg. 69:28-36 (July) 1954.

excised and these procedures were followed by end-to-end or side-to-side anastomosis. In the remaining case of the 9, the obstructing fibrous cord was excised. There were no operative deaths or serious postoperative complications in these 9 cases.

FRIEDMAN, J.: *Roentgen studies of the effects on the small intestines from emotional disturbances.* Am. J. Roentgenology, *72*, 367, Sept. 1954.

The significance of the fact that one can produce rapid alteration of the small intestinal mucosal pattern under roentgen observation by emotional disturbance requires critical evaluation. Cursory assessment might suggest that herein we have explained the mechanism by which patients so frequently have symptoms without evidence of organic disease in the intestine. Certainly this conclusion is not warranted from the facts that we have presented, only in a single case were the symptoms of the patient reproduced in association with the change in the mucosal pattern. In 2 of the 4 cases there was only a vague feeling of abdominal distress associated with the roentgen findings.

It is believed that these intestinal mucosal changes may conceivably appear in normal individuals who are questioned in a way to cause emotional distress such as anger, remorse, fear and frustration and are not necessarily of pathological nature.

The results of these studies, therefore, have only demonstrated that emotional distress per se can induce an altered mucosal pattern in the small intestine and that it is not necessary for the patient to be deficient in foodstuffs or chemicals.

Franz J. Lust.

ARON, E., NEZELOF, CH. AND GUESLE, J.: *Research concerning the pathogenesis of Shay's ulcer.* Archives des Maladies de l'Appareil Digestif, Volume 43, no. 5, May 1954, pages 496-504.

Recalling the work done by the French School, especially that of Debray and Laumonier, and of Lambling, the authors specify that the Ulcer of Pyloric ligature is not a direct result of gastric distention or peptic digestion.

The pylorus which is a "zone reflexogene" in the rat determines after traumation a neuro-vascular reaction in the stomach. An increase of capillary permeability determines sub-epithelial infarctions which communicate with the gastric lumen.

On this experimental basis, the authors demonstrate the protective effect of the vaso-dilators (nicotinic acid), the aggravating effect of Cortisone and Desoxycorticosterone, and the protective effect of the Soma atrophic hormone. These hormones exert a direct action, antiphlogistic or prophlogistic, on the gastric wall.

The "ganglio-plegiques" (Pendiomide) do not inhibit the appearance of ulcers. But the derivatives of Phenothiazine, especially Chlorpromazine (4560 R P), exert a total inhibition of the phenomenon. It is shown to be a localized action increasing the resistance to anoxemia and diminishing the vascular permeability.

On the other hand different interventions practiced concomitantly with pyloric ligature (adrenalectomy, unilateral and bilateral nephrectomy, castration) prove to be efficacious in preventing the phenomenon, the percentage of success being very variable. These results show that a specific influence should not be accorded to the different ablations of organs. It seems most likely to be a protective non-specific action which enters in the framework of general sympathetic effects.

The histological lesions of the liver, adrenals, and kidneys in the rat could be equally interpreted as the effect and not the cause of pyloric traumatism.

The authors do not think that Shay's Ulcer could be considered as an experimental ulcer capable of enlightening the pathogenesis of the human ulcer and they doubt the specificity of the numerous means of protection studied up to the present time.

Guy Albot.

LEGER, L.: *Splenoportography in the exploration of the spleen, the liver, the pancreas and the portal vein.* Soc. Nat. fr. de Gastroentérologie, 5 avril 1954.

The author, according to an experience of 80 explorations without any accident, is able to describe the aspects of normal splenoportographies and to class the pictures of pathological splenoportographies in different cases:

A venous obstacle to the portal circulation either truncular phlebitis of the portal vein, the acute thrombosis of which has been clinically identified with this method, or a compression or thrombosis of the splenic vein, specially in cases of pancreatic diseases, carcinoma or chronic pancreatitis.

A parenchymatous obstacle. The exploration of hepatic cirrhosis by splenoportography may be helpful for it gives an opportunity to judge the abundance of the intrahepatic venous ramification, of the collateral circulation, and of the development of a substitute circulation toward mediastinum and especially the esophagus.

A tumor of the liver. Hepatic metastases detection is extremely important for the surgeon. On an other hand, the identification and topographic localization of primary tumors of the hepatic gland will facilitate the indications of hepatic lobectomy.

Splenomegalies must be submitted to a routine exploration by splenoportography which will give information on vascular connections of the gland, richness of the collateral circulation and also on the etiology of the splenomegaly: venous obstacle on the portal circulation, hepatic parenchymatous obstacle.

Finally, the splenoportography constitutes an essential exploration in the choice of surgical indications of portal hypertension. It permits one to eliminate preoperative phlebographies and gives information on the presence of some obstacle on the spleno-portal trunk, its accurate localization and gives to the surgeon the ability of choosing knowingly between a truncular or a radicular porto-caval anastomosis.

CLOSED CIRCUIT

Newark, N. J.—Medical Communications, Inc., of Newark, New Jersey announces "Medicine Today," the first regularly scheduled closed circuit television series to be telecast monthly to 25 major cities throughout the United States.

"Medicine Today" telecasts will be owned and produced by Medical Communications, Inc., a new organization formed for this specific purpose by Paul Klemtner & Company, Inc., ethical advertising and marketing agency of Newark, New Jersey. Each monthly telecast will originate in a different major teaching medical center in this country and will visualize important advances in medical and surgical technics of immediate value to the practicing physician. The Committee on Audio-visual Education of the Association of American Medical Colleges has expressed interest in this project, and its willingness to lend advisory assistance to the publisher and the producer.

"Medicine Today" will be made available as an aid to post-graduate medical education through the sponsorship of leading manufacturers marketing products for use by the medical profession.

The first telecast of "Medicine Today" is planned for early 1955, following completion of the installation of reception equipment in the 25 viewing cities. Precise air time and the places at which "Medicine Today" may be viewed will be announced shortly.

CLISTIN MALEATE—A CLINICAL APPRAISAL OF A NEW ANTIHISTAMINIC

Unless new antihistamines are superior to those currently in use, there is little reason for introducing them. Under clinical investigation by the authors is a compound which appears to have the necessary advantages—low dosage, high degree of effectiveness, low incidence of side effects—to warrant extensive clinical use.

The study was conducted on 126 patients from private practice. All were suffering from severe allergic symptoms not relieved by other measures, and all were given Clistin. Of these patients, 113 had allergic rhinitis; 11 urticaria; 1 asthma; 26 allergic rhinitis and asthma; 1 allergic conjunctivitis.

Of those patients receiving the 4 mg. dose of the drug, 87 per cent noted some degree of relief, and in 47 per cent this relief was marked to complete. Of those receiving the 6 mg. dose, 80 per cent obtained some benefit, with marked to complete relief in 37 per cent. All patients taking larger doses received some relief.

Onset of action of the drug usually was 30 to 60 minutes; duration of action approximately 4 hours. Side effects were negligible. The most common was drowsiness, but in only 4 per cent was this sedation considered to be of moderate or severe degree. Drowsiness, when it did occur, seemed to disappear after a few days despite continued medication.

Although it has generally been found that the most potent antihistaminic drugs are moderately or highly sedative in action, results of this study indicate that this compound, known chemically as carbinoxamine maleate, is a potent antihistaminic agent with only weak sedative properties, and should be a useful adjunct in the treatment of allergic conditions.

CANCO NAMES LUECK NEW VICE PRESIDENT

Dr. R. H. Lueck, formerly general manager in charge of American Can Company's research and technical department, has been elected vice president in charge of the department, it was announced by William C. Stolk, president.

The scientist, who has been with the company for 32 years, will continue to make his headquarters in New York. The position to which he has been elected is a new one in the firm, Mr. Stolk said.

A graduate of Carroll College at Waukesha, Wis., Dr. Lueck received a master of science degree at the University of Wisconsin and started with American Can in 1922 as a research chemist in the firm's Maywood, Ill., laboratories. He later served as manager of the company's San Francisco laboratory and in 1934 was transferred to the Hawaiian Islands where he became manager of the company's operations.

Dr. Lueck was appointed manager of the research laboratory at Maywood, Ill., in 1936 and seven years later became director of research. He served as manager of sales for Canco's Pacific division between 1944 and 1950 when he was named general manager of the research and technical department in New York.

Dr. Lueck holds an honorary degree of doctor of science from Carroll College. Among the technical societies of which he is a member are: the American Chemical Society, the Institute of Food Technologists, the Institute of Chemists, the New York Association of Research Directors, the Industrial Research Institute and the American Association for the Advancement of Science.

He served as chairman of the can industry's technical committee for tin conservation during World War II and is the author of many scientific papers on canning technology and corrosion of tin plate.

FRED H. THISTLETHWAITE AND DONALD A. SWANSON GET PROMOTIONS AT PARKE, DAVIS & COMPANY

Detroit.—Promotion of Fred H. Thistlethwaite, 47, to a new administrative post as sales coordinator for Parke, Davis & Company was announced here recently by Graydon L. Walker, vice president and director of U. S. sales and promotion.

Thistlethwaite has been manager of hospital and biological sales since November, 1946, and will be succeeded by Donald A. Swanson, 30, who has been assistant manager since last May.

Parke-Davis has a domestic field sales of approximately 1,000 representatives who serve 200,000 physicians and pharmacists in 53,000 drug stores in the United States and Canada.

Thistlethwaite has been with the pharmaceutical firm more than 25 years. Born March 5, 1907, at Richmond, Ind., he was graduated from Purdue University in 1929 with a degree in biochemistry. He immediately joined the Parke-Davis research department and was transferred four years later to the sales department as a special biological detailist. In 1938, he went to Cleveland as a medical service and hospital representative and six years later, became field manager in the Detroit Branch. In 1945, he was promoted to assistant branch manager at Detroit. In 1946, he was

manager of medical service and correspondence for several months before his appointment as manager of hospital and biological sales. This year, Thistlethwaite was selected to attend the 26th Advanced Management Program at the Harvard University Graduate School of Business Administration from Sept. 15 through Dec. 3. He lives at 85 Colonial, Grosse Point Shores, Mich.

Swanson, born Feb. 26, 1924, at Ludlow, Pa., was graduated from the University of Michigan School of Pharmacy in June, 1949. He was employed by the Owl-Rexall Drug Company in Los Angeles from June, 1949, until January, 1950, when he joined Parke-Davis. Between 1950 and 1952, he was a sales and medical service representative for the Los Angeles branch. In 1952, he became Los Angeles area hospital representative, holding that post until his appointment as assistant manager of hospital and biological sales. He lives at 22952 Marter Road, St. Clair Shores, Mich.

ATOMIC ENERGY IN MEDICINE, PROTECTIVE MEASURES AGAINST RADIOACTIVITY DISCUSSED
WHO HOLDS FIRST INTERNATIONAL DISCUSSION IN THIS FIELD

The role of atomic energy in the development of medicine and biology, together with the responsibilities of WHO in this new field, were explored in Geneva at a meeting with 4 scientists invited by Dr. M. G. Candau, Director General of the World Health Organization. The discussions, held December 13-16, were led by Dr. John Bugher, Director of the Division of Biology and Medicine at the Atomic Energy Commission, Washington, D. C., with the participation of Dr. A. G. Cipriani, Director of Medical Research, Chalk River Project, Chalk River, Ontario (Canada), Dr. John F. Loutit, Director of Radiobiological Research Unit at the Atomic Energy Research Establishment, Harwell, England, and Professor Charles Manneback, Professor of Civics at Louvain University, Belgium.

The WHO consultants dealt with two main topics. The first included problems of health protection in dealing with atomic energy, the disposal of radioactive waste material, nuclear reactor safety, the definition of a radiological unit and the standardization of radioactive material; second topic was the constructive use of atomic energy in biology, medicine and public health

Discussion of the positive aspects of atomic energy centered on the use of radioactive isotopes in the diagnosis of various diseases and in medical research. The WHO consultants indicated fields in which the use of radioactive isotopes can lead to important discoveries, among them human biology, also diagnosis, treatment, epidemiology and the control of diseases.

Among other subjects discussed were nutritional problems, the solution of which depends greatly on advances to be made through the use of atomic energy in agriculture and fisheries.

The meeting of consultants was planned some time ago by the WHO but was given more urgency by a resolution adopted on 4 December last by the United Nations General Assembly, calling for an international conference on the peaceful uses of atomic energy and establishing immediately an advisory committee to prepare this conference. The assembly decided on a conference for the study in general of the development of atomic power and to consider in particular technical areas such as biology, medicine and radiation protection. The conference is to be held not later than next August.

Competent agencies, among them the World Health Organization, are to be called in consultation by the Advisory Committee and will participate in the conference. The discussions of the WHO consultants represent the first contact with four outstanding experts devoted to the medico-biological aspects of atomic energy and should make it possible for the WHO to contribute to the discussions of the Advisory Committee and to participate fully in the actual work of the international conference.

YELLOW FEVER ON THE MOVE; EPIDEMICS POSSIBLE
AREAS IN U. S. A. VULNERABLE TO BIOLOGICAL WARFARE

"Yellow fever is not a 'dead duck', it has not been conquered, it has not been eliminated as a permanent threat to the United States. Yellow fever has recently come back to nearby countries where it had been unknown for decades."

These were the words of Dr. Fred L. Soper, Director of the Pan American Sanitary Bureau, Regional Office of the World Health Organization, in reviewing the present status of this frequently-epidemic disease. Its extent in the Americas, in the light of its history and epidemiology, was reviewed at a conference of top-level experts that met in a two-day session in Washington last week, at the Bureau's invitation.

Yellow fever seems of little international importance or concern, Dr. Soper said, until it suddenly appears in a port city, as it did last summer in Port-of-Spain, Trinidad. Then the picture changes overnight, there is great excitement, urgent and often unreasonable measures are taken; past epidemics are recalled and interest in the disease as a public health menace rekindled.

Following an urban epidemic of yellow fever in 1928-29 in Rio de Janeiro, the capital of Brazil, twenty years after the disease had been controlled and at a time when no apparent threat of reinvasion existed, the Government embarked on a program to make all its cities and towns forever safe from this deadly scourge. The *Aëdes aegypti* mosquito, the only urban vector of yellow fever, has now been eradicated from all of the cities and towns of this huge country, larger by a tenth than is the United States.

This information was brought out in the course of the conference, which reviewed the successful eradication campaigns in neighboring countries with the aid and encouragement of the Brazilian Government as an insurance against reinfestation.

On the recommendation of Brazil, the Pan American Sanitary Bureau initiated in 1947 a Continent-wide campaign to help governments eradicate the *Aëdes aegypti* from the Western Hemisphere. Today all of Brazil, Paraguay, Bolivia, Chile, Ecuador and Peru have been declared free of this mosquito and the campaign is well advanced in the rest of South America. The eradication campaign has begun in Mexico, Cuba, Haiti, the Dominican Re-

public and in many Caribbean areas. In Central America, Panama, Costa Rica and Nicaragua have been declared free of *Aëdes aegypti* mosquitoes. But from there north the picture changes. Small infested areas are found in El Salvador and Honduras, and a much larger one in Guatemala. The *aegypti*-infested area continues solidly along all of the Atlantic and Pacific coastal regions of Mexico, flooding into the United States, the only country in the Americas harboring the *Aëdes aegypti* that has not yet joined in the eradication campaign.

A line drawn from Yuma, Arizona, to the northeast corner of New Mexico, then across the country to the Atlantic at the boundary between North Carolina and Virginia marks the northern limit of the presence of the urban yellow fever mosquito in the United States. That embraces the whole southern third of the country which has been declared by the U. S. Public Health Service a "receptive area" (i.e., open to the introduction and transmission of yellow fever).

Aëdes aegypti may be considered "domestic." In the Americas it inhabits only human dwellings in cities, towns and in rural dwellings, breeding in artificial water containers. It is therefore accessible to residual insecticides such as DDT, which have greatly facilitated eradication. Unfortunately there are other species of mosquitoes that also transmit the yellow fever virus; these live exclusively in tropical jungles. They are found throughout the whole tropical belt of the Hemisphere. They infect monkeys and probably certain marsupials, with yellow fever, thus keeping the virus alive and constituting a permanent reservoir and threat to humans who visit or live in the jungle areas. The only protection against the so-called jungle yellow fever is vaccination.

Jungle yellow fever is a direct problem of all the countries on the American mainland with the exception of Canada, the United States, Uruguay and Chile. It moves in waves, dying down as it kills off or immunizes the monkey population, only to move on and flare up again a few or many years later. Such a wave has been moving slowly but steadily up through Panama and Central America since 1948, reviving old memories of the devastating epidemics that preceded the building of the Panama Canal. The present wave reached the northwest corner of Honduras in September, 1954. Incidentally, no human case had been reported in Central America between 1924 and 1948.

This movement of jungle yellow fever northward is very significant and fraught with grave danger, because it has approached close to the areas in North America still infested with the dread urban carrier, *Aëdes aegypti*, the mosquito that can cause city epidemics. Once that small gap in Guatemala has been bridged, the threat of epidemics in cities and towns becomes immediate. Hence last week's conference, at which a comprehensive appraisal of the situation was made, and measures to meet it were studied. Highly qualified technical experts at the conference actually predicted the movement of jungle yellow fever northward until it links with towns infested by the domestic mosquito.

The discussions stressed the necessity for broader and more concerted action to eradicate the remaining foci of *Aëdes aegypti* from the Americas. No one country can consider itself safe when its neighbors have not cleaned house, one scientist pointed out, since mosquitoes do not respect frontiers. As long as jungle yellow fever exists, there is always the possibility of the movement of an infected person from a jungle area into a city or town infested with the urban mosquito during the six-day incubation period of the disease. Only when the eradication campaign becomes universal will all be freed of any fear of re-infestation.

Brazil's experience was emphasized as an example for emulation: after cleaning out the *aegypti* from urban centers, it was found more effective and cheaper to use the eradication crews to clean up the suburbs than to maintain a constant control in the cities. Then it proved more practical to extend the eradication to embrace every single house in the country, in every city and town, in every rural area. This led to Brazil's encouragement of neighboring countries and finally to the continent-wide campaign sponsored by the Bureau, well illustrating the old adage of an ounce of prevention.

Colonel Norman W. Elton, Director of Medical Laboratories at the Army Medical Center in Edgewood, Maryland, pointed out an added danger to the United States: biological warfare. An enemy, he said, could introduce yellow fever virus into the southern part of the United States and *Aëdes aegypti* there would do the rest to spread this highly fatal disease in its most virulent form.

Indicating that this was not mere academic speculation, the conferees were reminded that during World War II, The Rockefeller Foundation laboratories and others located in various parts of the world kept yellow fever virus under lock and key to prevent its falling into the hands of an enemy who might develop it for use in biological warfare.

Various gaps in our knowledge regarding yellow fever and its spread were brought out during the discussions. There is uncertainty as to the number of species and possible sub-species of jungle mosquitoes that transmit yellow fever. There may even be other insect vectors of this disease. There are questions to be answered regarding the animal reservoir that keeps the virus alive in the jungle. Monkeys are a known reservoir. Marsupials are strongly suspected. There may be others. The "quiet" periods between yellow fever outbreaks are not too well understood: the survival of the virus, possibly in mosquitoes, during dry seasons when the mosquitoes seem to disappear, only to spread the disease anew a couple of months after the start of the next rainy season. Does the mosquito, together with the virus, hibernate or "estivate" during the "quiet" period? A number of other highly technical problems remain to be studied in the fight to conquer yellow fever.

There is, for example, the problem of vaccines. There has yet to be developed a satisfactory heat-resistant yellow fever vaccine. The one in use in the Americas today requires refrigeration—a major obstacle in carrying out vaccination campaigns in the less-accessible jungle country where it is most needed.

To meet these problems, the con-

agents of choice

for the treatment of ***pneumonia*** *and other respiratory tract infections*

Terramycin®

BRAND OF OXYTETRACYCLINE

For (ESTABLISHED) broad-spectrum antibiotic therapy—supplied in convenient Capsules, Tablets (sugar coated), Oral Suspension (raspberry flavored), Pediatric Drops (raspberry flavored), Intramuscular, Intravenous, Ophthalmics, Ointment and other topical forms.

Tetracyn®

BRAND OF TETRACYCLINE

For the (NEWEST) broad-spectrum antibiotic therapy—supplied in convenient Capsules, Tablets (sugar coated), Oral Suspension (chocolate flavored), Pediatric Drops (banana flavored), Intramuscular, Intravenous, Ophthalmic and Ointment.

Both discovered by **Pfizer** *world's largest producer of antibiotics*

PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

ference was unanimous in the need for more extensive and more intensive research. Strongly advocated was the setting up of a mobile field laboratory in the expected path of the jungle yellow fever wave moving north through Honduras. A region of tropical forest country in north central Guatemala was proposed as the probable path and the logical location for such a laboratory. It would be staffed with the necessary specialists and equipment and would be invaluable in the study of an outbreak of the disease at its inception. All aspects of the disease could be studied from the beginning to the end of the outbreak, including the insect vectors, the animal and perhaps human victims, and what goes on during the "quiet" periods. The use of a helicopter based at the field laboratory would be most useful, it was agreed.

The Pan American Sanitary Bureau has taken these suggestions under advisement.

It was also agreed that laboratories now working on yellow fever problems and producing vaccine, such as the Oswaldo Cruz Institute of Rio de Janeiro and the Carlos Finlay Institute in Bogota, and the important research center in Panama, the Gorgas Memorial Laboratory, should be given more technical aid and financial encouragement to extend the study of the disease. The newly-established Tropical Virus Laboratory in Trinidad can also contribute materially in yellow fever research, it was indicated.

The general consensus of the meeting was that the danger is so real and so close that more of the laboratory and research facilities of governments and of endowed institutions should be engaged in this important study and that the results should be pooled. More coordinated efforts throughout the Continent in research and eradication programs were urged.

The last epidemic of yellow fever in the United States was in New Orleans in 1905. This year's outbreak in Trinidad followed forty years absence and involved *aegypti*-infested Port-of-Spain, the first maritime port in the Americas to report yellow fever in twenty-five years.

The alarm caused by this flare-up and by the current movement of jungle yellow fever to areas within reach of the United States tends to emphasize the long-term, permanent nature of the yellow fever problem.

Even after the present northward movement completes its cycle, the threat of urban epidemics of this highly fatal disease will remain for *aegypti*-infested communities indefinitely, since there is no feasible method of getting rid of the permanent source of infection in the tropical forests.

The conference emphasized that the first and most urgent step for the United States is the complete eradication of *Aëdes aegypti*, both in self-protection and to protect neighboring countries from re-infestation.

The second step, stressed as an equally important one if the global story of yellow fever is to be ended, is the long-term mobilization of our research and technical forces to fill in all the present gaps in our knowledge of the disease, its vectors, its animal hosts and the methods for its eventual eradication.

SYMPOSIUM ON THE ANTIMETABOLITES—THEIR MODES OF ACTION AND THERAPEUTIC IMPLICATIONS

(Tuesday, March 1, 1955, The Biltmore Hotel, New York City)

Morning Session

Chairman: Dr. Paul L. Day, University of Arkansas, Little Rock, Arkansas.

1. Anti-Vitamin E Stress Factors as Related to Fatty Peroxides. E. L. Hove, Alabama Polytechnic Institute, Auburn, Alabama.

2. Thiamine Antagonists. L. R. Cerecedo, Fordham University, New York, New York.

3. Vitamin K. Antagonists. K. P. Link, University of Wisconsin, Madison, Wisconsin.

4. Folic Acid Antagonists. J. H. Burchenal, Memorial Center for Cancer and Allied Diseases, New York, New York.

Afternoon Session

Chairman: Dr. R. W. Heinle, The Upjohn Company, Kalamazoo, Michigan.

1. Purine and Pyrimidine Antagonists. G. H. Hitchings, The Wellcome Research Laboratories, Tuckahoe, New York.

2. A Naturally Occurring Antimetabolite of Methionine in the Causation of a Disease. D. W. Woolley, The Rockefeller Institute for Medical Research, New York, New York.

3. Pantothenic Acid Antagonists. O. D. Bird, Parke, Davis & Company, Detroit, Michigan.

4. Vitamin B_6 Antagonists. W. W. Unbreit, Merck Institute for Therapeutic Research, Rahway, New Jersey.

5. Riboflavin Antagonists. J. P. Lambooy, The University of Rochester, Rochester, New York.

FOR CRIPPLED PERSONS

Chicago.—An outstanding opportunity to professional workers with the handicapped for specialized training in counseling and placement of crippled persons in self rewarding jobs is announced today by the National Society for Crippled Children and Adults, the Easter Seal Society.

Alpha Gamma Delta, international women's fraternity, in cooperation with the National Society, for the eighth consecutive time will grant from 15 to 20 fellowships with training to be given at the Institute of Physical Medicine and Rehabilitation of New York University-Bellevue Medical Center June 20 to July 15, 1955.

The deadline for receipt of applications for these fellowships is March 15. Fellowships will cover tuition and a moderate amount of other expenses. They will be awarded to qualified counselors, guidance teachers, employment interviewers, placement personnel, and other professional persons working with the handicapped.

The course will include lectures and demonstrations in aspects of physical rehabilitation for the disabled including those with cerebral palsy. Instruction will be provided by members of the staff of the Institute of Physical Medicine and Rehabilitation, New York University School of Education, and other specialists in the field.

Six points of academic credit at the graduate level will be given to those who successfully complete the program. Selection of persons to receive the fellowships will be made on the basis of an evaluation of candidates with the highest qualifications who are working for schools, agencies, business or industry or

are able to make a contribution toward effective counseling and placement work for the handicapped.

Application forms and other information may be secured from the Personnel and Training Service of the National Society for Crippled Children and Adults, 11 South La Salle Street, Chicago 3, Illinois.

TAINTER ELECTED PRESIDENT OF ACADEMY OF SCIENCE

Dr. M. L. Tainter, director of the Sterling-Winthrop Research Institute, has been elected president of the N. Y. Academy of Science for a one-year term ending December 1955, it was announced by the Academy.

The election of officers and announcement of award winners took place over the week-end, during the 137th annual meeting here of the organization. The Academy is the nation's fourth oldest scientific society.

Dr. Walter S. Root, professor of physiology, College of Physicians and Surgeons, Columbia University, was named president-elect of the group. Elected as vice presidents were Prof. William H. Cole, Rutgers University, and Ross S. Nigrelli of the N. Y. Zoological Society. Julius Bird, assistant curator, American Museum of Natural History, was re-elected corresponding secretary; Charles W. Mushett, Merck Institute for Therapeutic Research, recording secretary; Richard O. Roblin, American Cyanamid Company, treasurer.

One of the country's leading pharmacologists, Dr. Tainter, has been director since 1946 of the Sterling-Winthrop Research Institute, Rensselaer, N. Y. He was formerly head of the Division of Physiological Sciences at the College of Physicians and Surgeons, San Francisco, and professor of pharmacology at Stanford University Medical School. He received his A.B., M.A. and M.D. degrees from Stanford, and an honorary D.Sc. degree from R. P. I.

Dr. Tainter is a member of numerous professional groups, including the American Society for the Advancement of Science, American Medical Association, American Society of Pharmacology and Experimental Therapeutics, International Association of Dental Research, American Chemical Society and American Foundation for Tropical Medicine.

Two honorary life members were elected to the Academy at its annual meeting. They were: Dr. Ulrich R. Evans, British author, who will receive the 1955 Palladium Medal of the U. S. Electrochemical Society, and Dr. Emmanuel Saure-Fremiet of Paris.

The Wenner-Gren Foundation Award of $1,000 was given to Dr. Raymond B. Cattell, research professor at the University of Illinois Laboratory of Personality Assessment.

ANTIBIOTICS

Detroit.—John L. Bach of Chicago, director of press relations for the American Medical Association, said here that "for the patient, an-

tibiotic drugs are a bargain at any price."

"Antibiotics have not only cancelled out many of the once-fatal diseases," he said, "but they have eliminated entirely many of the bread-and-butter diseases which kept doctors so busy years ago."

Speaking at a year-end meeting of 125 key executives of Parke, Davis & Company from the U. S. and Canada at the Sheraton-Cadillac hotel Dec. 13, Mr. Bach said there was a need for a long-range educational program by drug manufacturers to acquaint the public with the outstanding results in antibiotic development.

"Five dollars worth of penicillin can eliminate the need for a $150 mastoid operation and $200 in hospital bills," Mr. Bach said, and then added: "Does the public know this?"

The A.M.A. spokesman contrasted the treatment of pneumonia today with the problem faced by the horse and buggy doctor not so many years ago.

"When the old family doctor was called to see patients with pneumonia, he was forced to sign 33 death certificates out of every 100 patients seen. In addition to the number of deaths caused by pneumonia in that day, there were incalculable man-hours lost by prolonged illness and convalescence, which that wonderful old family doctor was powerless to overcome. The cost of medical care for pneumonia patients then was not only high, but the cost in lives and in man-hours lost in prolonged convalescence was tremendous indeed.

"The antibiotics changed this picture completely. Out of every hundred pneumonia patients seen by a doctor today, he will sign not 33 but only one, or at the most, two death certificates. The man-hours lost in convalescence have, for the most part, been largely eliminated."

Mr. Bach said that "when a life is at stake, the cost of any drug or drugs should be a minor consideration."

"Compared with early prices," Mr. Bach said, "antibiotic prices today are inordinately cheap. In 1944, penicillin cost $20 for an average dose of 100,000 units. Today, it is anywhere from two to eight cents for the same amount. Streptomycin came on the market at $15 a gram. Today, the same amount can be bought for 15 cents. Some of the more recently developed antibiotics in the 'broach spectrum' group have been cut 50 per cent in price."

"Is the public fully aware of this downward trend?" Mr. Bach asked. He urged all pharmaceutical manufacturers to "tell the public your marvelous story of antibiotic development."

He said that if all drug manufacturers create a better understanding of what they are doing, how they do it, why they do it—and make clear who profits thereby—the cumulative effort will be irresistible. The situation, amid today's cry of high prices, demands the best efforts of the industry. If the industry makes the effort, and attains at least part of the objective, much will be accomplished in erasing the common belief that drugs generally are too costly."

OLDEST "TEAM" IN PHARMACEUTICAL ADVERTISING FIELD TO BE SPLIT UP BY RETIREMENT OF WALTER M. CHASE

Detroit.—For the first time in 34 years, the two men who have been responsible for thousands of Parke, Davis & Company advertisements in national magazines and professional journals will be separated Dec. 31 by the retirement of Walter M. Chase.

Chase, as associate, and Ralph G. Sickels, as director of advertising, have been together since 1920 and now are the oldest such "team" in the pharmaceutical industry. They both joined the company on the same day, Sept. 28, but six years apart—Chase in 1914 and Sickels in 1920. Chase was the first man Sickels saw at Parke-Davis, and they've been working side by side ever since.

Now 66, Chase is still active and intends to remain that way at something, perhaps travel. Next fall, for example, he intends to drive to South Bend, Ind., and see the Notre Dame football games with Mrs. Chase and their daughter, Doris Ann, who is employed in an insurance firm and also is studying law. Meanwhile, Chase expects to spend considerable time watching television at their home, 1254 Bishop Road, Grosse Point Park, Mich.

RECEIVED SOME OF PHARMACY'S HIGHEST HONORS

Chase is completing a three-year term as an elected member of the national council of the American Pharmaceutical Association, one of the highest honors in pharmacy. He is a life member of the A.Ph.A., with which he has been affiliated since 1915. The Maine Pharmaceutical Association made him an honorary life member for his part in the "Know Your Pharmacist" series of Parke-Davis advertisements.

He is past president of the Michigan Branch, A.Ph.A., and a director and past president of the Michigan Academy of Pharmacy.

The national Parke-Davis advertisements, stressing "See Your Doctor" and "Know Your Pharmacist" themes, and the professional journal messages about products reach every physician and druggist in the United States and Canada.

Parke-Davis is one of the largest users of journal space in the pharmaceutical manufacturing field. Chase had had charge of advertising in over 200 different medical, hospital, drug and related publications. It has been estimated that each month every U. S. physician sees a minimum of half a dozen journals in which Parke-Davis ads appear—and many see even more, and at more frequent intervals. Every pharmacist, at least four times a month, sees a Parke-Davis message in the journals reaching him.

EDUCATED IN MAINE BEFORE COMING TO MICHIGAN

Born July 2, 1888, at Bangor, Maine, Chase received a B.S. degree from the University of Maine College of Pharmacy in 1910. He spent several years getting retail pharmacy experience before joining Parke-Davis. During World War I, he served as a medical supply officer in the U. S. Army. He is a past commander of Turnverein, Post 291, American Legion, and a member and past chaplain of Parke-Davis Post 469.

Sickels, discussing Chase's retirement, said, "We're going to miss him around here."

He paused and added, "That's the understatement of the year."

visceral eutonic

DACTIL

PLAIN AND WITH PHENOBARBITAL

relieves **pain⇄spasm** usually in ten minutes

DACTIL relieves gastroduodenal or biliary pain so quickly that you can usually see it work right in your office.

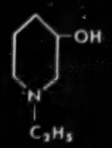
DACTIL capsules act at the site of visceral pain—relieve pain ⇄ spasm within minutes and control spasm within two days. Unusually well tolerated, DACTIL does not interfere with gastrointestinal or biliary secretions, normal tonus or motility.

TWO FORMS *Q I D*

DACTIL with Phenobarbital in bottles of 50 capsules. There are 50 mg. of DACTIL and 16 mg. of phenobarbital (warning: may be habit-forming) in each capsule.

DACTIL (plain) in bottles of 50 capsules. There are 50 mg. of DACTIL in each capsule.

DACTIL, first of the Lakeside piperidol derivatives, is the *only* brand of N-ethyl-3-piperidyl diphenylacetate HCl.



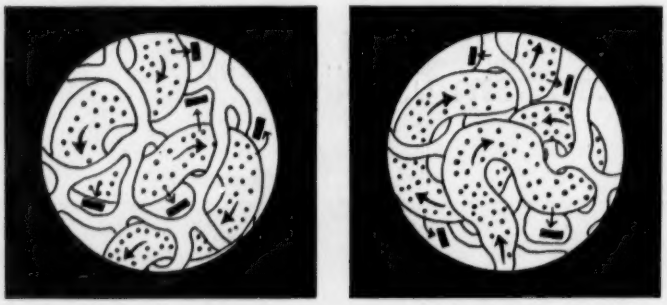
Lakeside Laboratories, INC. · PIONEERS IN PIPERIDOLS · MILWAUKEE 1, WISCONSIN

MICTINE*—THE NEW ORAL DIURETIC

Searle MICTINE Provides Effective Oral, Non-Mercurial Diuresis

The result of many years of research, Mictine, brand of aminometramide, supplies a long-felt need for an improved oral diuretic. Mictine, 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione, is not a mercurial, xanthine or sulfonamide.

Effectiveness: Every method for measuring the diuretic effect in man now available, including precise human bioassay studies, without exception demonstrated that Mictine is an effective oral diuretic, and these studies show that approximately 70 per cent of *unselected* edematous patients treated with Mictine by mouth respond with a satisfactory diuresis.



Mictine is believed to act by the selective inhibition of the reabsorption of sodium ions. Thus, the resulting diuresis is characterized by increased quantities of sodium ions and water.

Well-Tolerated: There are no known contraindications to Mictine, even in the presence of hepatic or renal damage, and there is no risk of acidosis. On high dosage, Mictine causes some side effects in some patients but on three tablets daily these side effects (anorexia and nausea, rarely vomiting, diarrhea or headache) are minimal or absent.

Indications: Mictine is useful primarily in the *maintenance* of an edema-free state and in the *initial and continuing* control of patients in mild congestive failure. Mictine may be used also for *initial and continuing* diuresis in *more severe* congestive states, particularly when mercurial diuretics are contraindicated.

Administration: The usual dosage for the average patient is one to four tablets daily with meals, in divided doses on an interrupted schedule. An interrupted dosage schedule may be accomplished by giving the drug on alternate days or for three consecutive days and then omitting it for four days.

For severe congestive states the dosage is four to six tablets daily with meals, in divided doses on interrupted schedules similar to those already mentioned.

Supplied: Uncoated tablets of 200 mg.

**Trademark of G. D. Searle & Co.*

SEARLE